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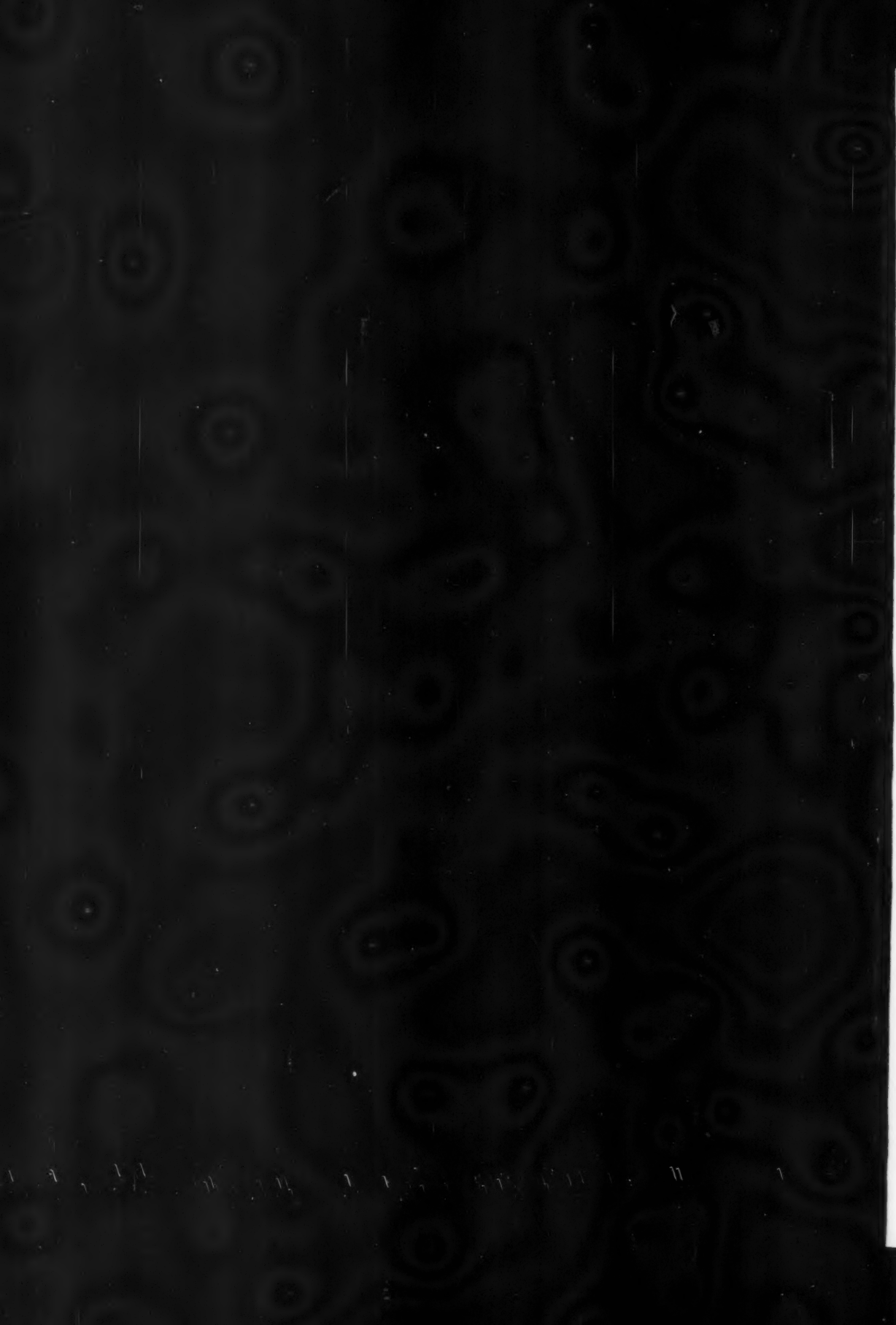

RADIOLOGICAL DIAGNOSIS OF RHEUMATIC PERICARDIAL EFFUSION

BY

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Received August 8, 1952

Twenty-one cases of rheumatic pericardial effusion have been studied in order to determine the precise nature of the radiological signs, including their frequency and the time of their appearance. The effusion recurred in two cases so that twenty-three episodes have been investigated in all. In fifteen the effusion developed after, and in the remainder before the patients were admitted. Seven of the patients died when effusion was still present. It was possible to study the radiological signs of fifteen effusions as they developed and of fourteen as they subsided. Proof of the diagnosis was obtained in twelve cases; at autopsy in seven and by cardiac catheterization in five: of the remaining nine, typical electrocardiographic changes occurred in five, pericardial fluid was aspirated from one, and convincing clinical signs of effusion were found in all. The course of the electrocardiographic and clinical signs followed the same pattern that was observed in the cases of pericardial effusion proven by autopsy or catheterization.

Signs of Developing Pericardial Effusion

Rate of increase in size of heart shadow. The rate of change in the size of the cardiac silhouette could be determined in 13 of the 15 cases. Generally, the cardiothoracic ratio increased rapidly to attain its maximum within a few days: it increased from a mean of 54 to 68 per cent during a period of eleven days, this being the average time for the effusions to reach maximum size (range, 4 to 25 days). The mean difference was 13·7 per cent (S.D. 6·5%). A significant change in cardiothoracic ratio was amongst the first major radiological signs of effusion in all cases.

Shape. A sudden change in shape was apparent in most cases: the normal sub-division of the silhouette became obliterated and the whole cardiac shadow assumed a more spherical appearance. The shape resembled that of a pear, carafe, or onion in different cases, depending on the size of the effusion. This change was amongst the early signs of effusion in ten and amongst the later signs in five.

Obliteration of the normal contours of the left border always occurred early: it resulted in the appearance of a straight left border extending upwards to include the lower segment of the aortic knuckle. With large effusions the left border developed a smooth convex bulge in its upper half, this change being of diagnostic value in four cases which already had straight left borders prior to the onset of their present attack of pericarditis. A change in shape of the left border was one of the first signs of effusion in fourteen cases.

A change in shape of the right border occurred fourteen times and was one of the first radiological signs of effusion ten times. The right cardio-diaphragmatic angle remained unchanged in eight, became more acute in four, and less acute in two cases at the same time as the shape of the right border changed.

Other signs. Disappearance of the shadow of the first part of the descending thoracic aorta was amongst the early signs of effusion seven times and amongst the later ones once. In the remaining seven the shadow had not been seen prior to the onset of pericarditis.

A mean increase of 42 per cent (S.D. 9·4%) of the initial width of the vascular pedicle, due to dilatation of the superior vena cava, occurred in twelve cases and was amongst the first signs of effusion in seven of them.

The outline of the posterior border of the heart shadow was always indistinct in the oblique views. In one this appearance preceded the onset of the present pericardial episode; in eight it occurred early in the development of the effusion, and in the remaining four later. In four cases the oblique views showed a hazy posterior outline at a time when the pericardial effusion was still small and before pleural effusions had developed (Fig. 1), so this haziness could not be attributed either to pleural effusion or to a massive pericardial effusion.

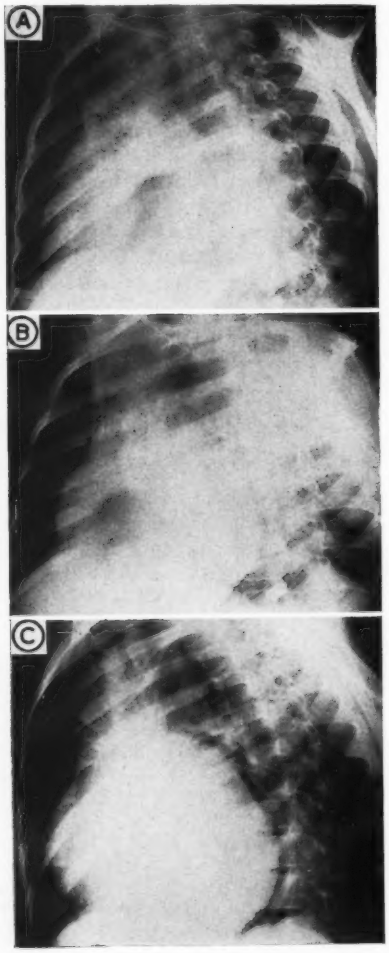

FIG. 1.—Hazy posterior cardiac border (A) at height of effusion, (B) during resolution of effusion, and (C) contrasted with second oblique view in a case of cardiac enlargement.

Details of the order of development of the individual signs are shown in Table I. Thus the radiological signs which were of most value in making a diagnosis of pericardial effusion were (*a*) a rapid increase in the transverse diameter of the heart shadow, and (*b*) straightening of the left border.

These were present in all cases and were generally the earliest signs. The following signs were of secondary value; they were not always present and often appeared only at a later stage: change in the general contour, changes in the right border, increase in width of the vascular pedicle, disappearance of the shadow of the first part of the descending aorta, and haziness of the posterior border of the heart shadow in the oblique views.

DISCUSSION

Our findings that straightening of the left border and a rapid increase in cardiothoracic ratio are the earliest radiological signs of pericardial effusion are in conformity with those of most previous authors (Holmes, 1924; Freedman, 1939; Roesler, 1943; Fenichel and Epstein, 1946). We did not observe any consistent change of the right cardio-diaphragmatic angle as described by Johnson and Palmer (1932) and Roesler (1943): they stressed the acuteness of the angle in effusion but in over half our cases it remained unchanged as the effusion developed.

An increase in width of the vascular pedicle occurred in 13 of our 15 cases, and was an early change in 7 of them. We have found only two authors who attribute significance to this sign, namely Smith (1935) and Friedberg (1950). Others (Freedman, 1939) have only noted shortening of the pedicle. However, widening in the supine position has been described by Schwedel (1946).

Increased density of the cardiac shadow with disappearance of the line of the descending aorta has been but rarely quoted in recent years, save by Oosthuizen (1943). The limited value of this sign is illustrated by the fact that seven of our cases showed it before the onset of their present pericardial effusion.

Haziness of the posterior cardiac border in the oblique views occurred frequently in our series. This sign was described by Roesler with very large effusions, but was often seen by us when the effusion was still small.

TABLE I

SIGNS OF DEVELOPING PERICARDIAL EFFUSION (15 CASES)

Time of development	Increase of cardio-thoracic ratio	Straighten-ing left border	Change of whole contour	Bulging right border	Increased width of pedicle	Disappearance of first part of descending aorta	Hazy oblique
Early	13	14	10	10	7	7	8
Late	0	1	5	4	5	1	4
Present before effusion ..	0	0	0	0	0	7	1
Unchanged ..	0	0	0	1	3	0	0

SIGNS OF REGRESSION OF PERICARDIAL EFFUSION

The rate of decrease in the size of the heart shadow could be determined in 13 of the 14 cases. Table II illustrates the sequence of resolution of these signs of effusion. The rate of decrease was less rapid than had been the rate of increase: there was a decrease of cardiothoracic ratio from a mean 70 to 57 per cent over a period of thirty-five days, showing a mean difference of 13 per cent (S.D. 5·4%), as compared with a 14 per cent increase in eleven days. Nevertheless, a change in size was among the first radiological signs of resolution in all cases. Of seven patients who had been observed from the onset of their pericarditis, four showed a complete regression of heart size. The remainder had residual increases in cardiothoracic ratios of 3, 4, and 7 per cent.

During recovery, a mean decrease to 75 per cent (S.D. 7·2%) of the previous width of the vascular pedicle was seen in 13 cases and in 12 of them it was an early sign of regression.

Eleven cases had shown indistinct posterior cardiac borders in the oblique views: in ten of them the borders returned to normal, six at an early stage of resolution. The right cardiac border had been abnormal in twelve and in five the contour showed an early return to normal. The right cardio-diaphragmatic angle remained unchanged in seven, became more acute in four and less acute in one, as the right border reverted.

The disappearance of the typical pericardial contour occurred early in six of the fourteen cases. Straightening of the left border, which had been present in all cases, persisted until late in most and did not revert to normal in three. The shadow of the descending aorta, which had disappeared in all, reappeared in only half of them and was a late sign of recovery in five.

TABLE II

SIGNS OF REGRESSION OF PERICARDIAL EFFUSION (14 CASES)

Time of regression	Decrease of cardio-thoracic ratio	Decrease of vascular pedicle	Hazy oblique	Decrease of right border	Restoration of normal contour	Changing left border	Reappearance of descending aorta
Early	13	12	6	5	6	2	2
Late	0	1	4	7	8	9	5
No return to normal ..	0	0	1	0	0	3	7
Never abnormal	0	1	0	2	0	0	0

Thus the earliest sign of regression was a reduction in cardiothoracic ratio. This was followed by return to normal of the vascular pedicle, the posterior cardiac outline in the oblique views, and the right border. Straightening of the left border and absence of the shadow of the descending aorta tended to persist, and sometimes did not return to normal.

The Effect of Posture

The effect of posture on the pericardial contour was first noted by Williams in 1903. When there is an effusion, skiagrams taken with the patient recumbent have been reported to show characteristic changes in cardiac contour. Thus Holmes (1924) found the heart shadow to be rectangular in this position, and White (1944) found it to be globular. Lewis (1942) and Schwedel (1946) considered the horizontal position to be of value only for demonstrating a change in shape of the left border. There appears to be little agreement as to the diagnostic value of these postural effects on the cardiac contour. Widening and shortening of the pedicle in recumbency was described by Schwedel (1946), Levine (1945), and Arendt (1948). We have found similar changes in cases without effusion. The recumbent lateral view showed significant displacement of the heart shadow with effusions according to Roesler, but Arendt found this position of little value.

In 1943 Oosthuizen described the sign of divergent vascular shadows in cases of pericardial effusion skiagraphed in the recumbent position—shadows extending upwards and laterally on both sides of the superior mediastinum. We have found that this sign is best seen when the patients are tilted head downwards. We have, therefore, taken skiagrams (antero-posterior at three feet) with the patient tilted head downwards at 45° and compared them with films taken head upward at 45°.

Thirty cases have been investigated: eleven with pericardial effusion, two with possible pericardial effusion: twelve with large hearts from established valve lesions and five with cardiac enlargement and a previous history of pericarditis. The sign was positive in 8 of 11 cases with undoubted effusion (Fig. 2) but also in 4 of 17 with cardiac enlargement. The presence or absence of the sign could not be closely correlated with the height of the venous pressure: all the 11 with effusion had a raised venous pressure, but three did not show this sign, and two of the four cases of enlargement with divergent shadows had normal venous pressures. When positive in cases of effusion, the sign had always been preceded by other radiological evidence. Widening of the vascular pedicle occurred in 10 of the 11 with effusion when tilted head downwards. It also occurred in 8 of the 17 with cardiac enlargement.

It is concluded that these two effects of posture on the shape of the cardiac shadow are of limited value in distinguishing between pericardial effusion and cardiac dilatation.

Retrospective Diagnosis of Effusion

In the light of these observations, the skiagrams of all previous cases that had been diagnosed as having generalized cardiac enlargement from established valve lesions were reviewed, lest any of them should show similar evidence of pericardial effusion. Retrospective diagnoses of effusion were made in 6 of the 75 cases reviewed. The skiagrams on admission in these six all showed many of the characteristic features of effusion: a typical pericardial contour with a straight left border, altered shape of the right border, an increased vascular pedicle, and absence of the shadow of the descending aorta. Indistinct posterior borders were seen in those cases in which oblique views had been taken. Subsequent skiagrams in all six cases showed a decrease in size and a return to more normal contours. Two cases had previously been in other hospitals and X-rays obtained later from these hospitals showed undoubted effusions.

Five other cases had large heart shadows with contours somewhat suggestive of effusion, but none of them had a straight left border or widening of the vascular pedicle and all had clear posterior cardiac bordres in the oblique views. They were regarded, therefore, as having cardiac enlargement from established valve lesions and not pericardial effusion. All five were observed over a period of one year or more and no changes were observed in heart size or shape. Two were catheterized and showed no evidence of effusion.

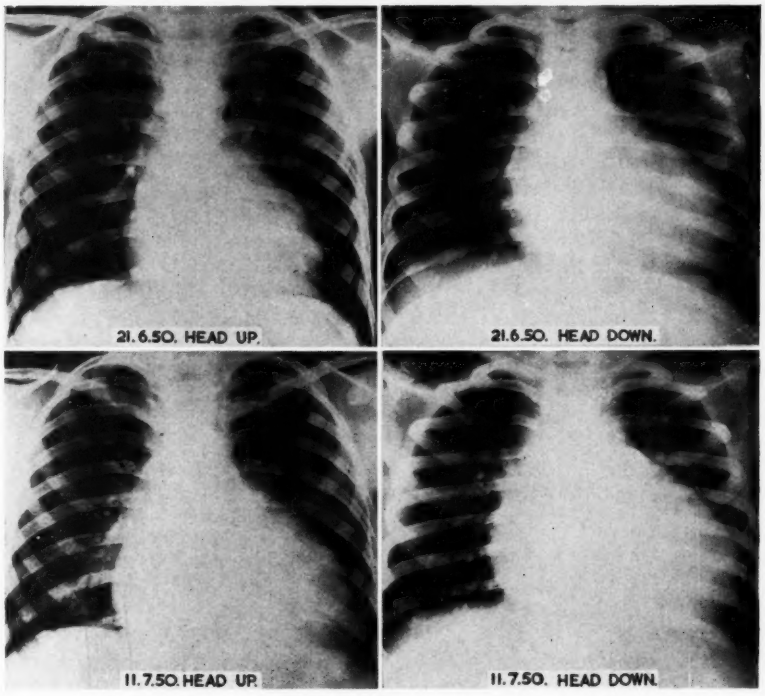

FIG. 2.—Tilt skiagrams taken before and after onset of effusion, showing development of divergent vascular shadows.

INCREASE IN HEART SIZE FROM CAUSES OTHER THAN EFFUSION

In the absence of pericarditis, the heart shadow increased in size during the period of observation in only 9 out of 215 consecutive cases with carditis. All of them had established valve lesions and active rheumatism, and one had signs of heart failure as well. In only one of the eight cases without failure was the rate of increase of size (5% in two weeks) in any way comparable to that which had been observed in effusion. In the case with failure, however, the rate of increase was more rapid, but could not be assessed accurately. In our experience, therefore, a rapid increase in heart size is due either to pericardial effusion or to congestive heart failure from active rheumatism and established valve lesions. We agree with Parkinson (1949) that it does not occur from dilatation alone in cases of early carditis. Keith and Brick (1942) reached conclusions similar to ours.

SPECIAL TECHNIQUES FOR THE DIAGNOSIS OF PERICARDIAL EFFUSION

Despite attention to points that have been emphasized in this paper, the differential diagnosis between pericardial effusion and cardiac enlargement is often difficult, particularly when the patient is first seen and before serial skiagrams are available. Various special techniques have been employed in view of this difficulty. The effect of position on the cardiac contour has already been discussed and is of little value. Fluoroscopy in our experience has failed to show any significant reduction of pulsation in the presence of an effusion. Pericardial paracentesis may, of course, be undertaken, but failure to obtain fluid does not exclude effusion owing to the frequency of early organization and loculation in some cases, and the mere demonstration of a few drops of fluid in

the pericardial sac does not necessarily indicate a significant effusion. Complete aspiration or partial removal of an effusion followed by air or lipodal replacement might provide more acceptable evidence, yet may well be thwarted by the loculations. As therapeutic aspiration is rarely necessary and the presence or early organization increases the hazards, diagnostic pericardial paracentesis has rarely been employed by us. Angiocardiography (Williams and Steinberg, 1949) would appear to be contra-indicated in acutely ill children.

Recently, cardiac catheterization has been employed in the diagnosis of pericardial effusion (Wood, 1950, 1951). We have used this technique in several of our cases and have found it to be of great value. Under visual control the catheter is passed into the right atrium and is then curled or looped so that the tip rests firmly against the lateral wall of the atrium. If there is then no opacity between the catheter tip and the lung field, no effusion can be present at this border. When a band of opacity separates the two, 7 to 10 ml. of diodone may be injected through the catheter, and skiagrams taken before and immediately after completing the injection: the dye then outlines the inner border of the lateral wall of the right atrium, and a pericardial effusion is seen as a shadow to the right of the catheter tip and the outlined atrial wall.

Fifteen cases of pericarditis have been investigated in this manner; two of them had undoubted large effusions, and were catheterized in order to confirm the value of the technique. Six of the remaining 13 had active rheumatism and cardiac enlargement, but it was not clear from routine skiagrams whether effusions were present or not. The catheter technique demonstrated a pericardial effusion as the main cause of the enlargement in all six (Fig. 3), and this was confirmed by

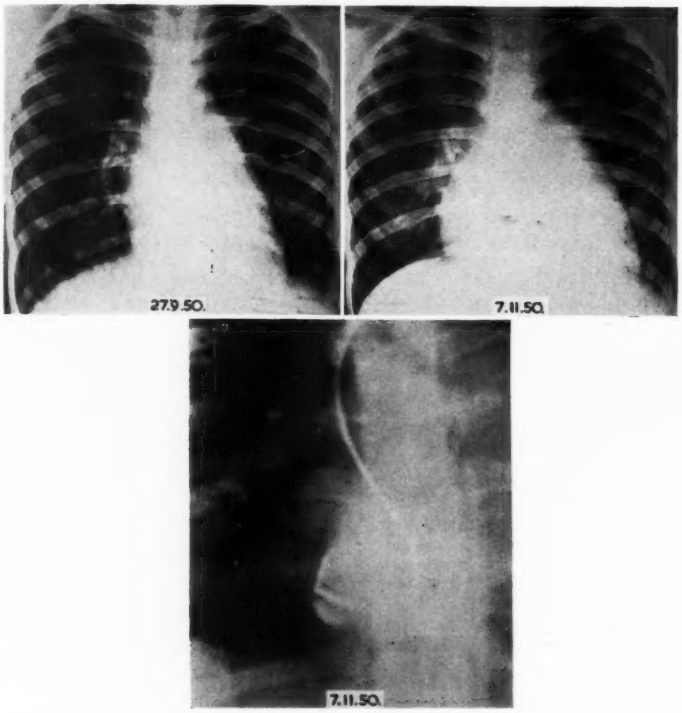

FIG. 3.—Skiagrams showing increase of cardiothoracic ratio of uncertain ætiology. Cardiac catheterization with diodone injection, demonstrating pericardial effusion.

their subsequent clinical and radiological course. Two of these patients subsequently died, and in both there was evidence of pericarditis at autopsy. In five others, also with active rheumatism and cardiac enlargement, the presence of effusion was suspected on routine skiagrams but was thought to be unlikely. Catheterization demonstrated only small effusions in all of them, and subsequent serial skiagrams confirmed that true cardiac enlargement was in fact present. Two were catheterized after their effusions had apparently receded, and some residual effusion or pericardial thickening was demonstrated in both. Catheterization of these children proved to be perfectly safe and caused no distress provided adequate preliminary sedation had been employed.

We have also investigated two cases of mitral incompetence with aneurysmal dilatation of the left atrium. On fluoroscopy both showed systolic expansion of the atrium visible on the right and left borders of the heart in the postero-anterior view. Catheterization of these cases also showed a shadow to the right of the catheter tip. However, this shadow lies at a higher level than that of a pericardial effusion (Fig. 4) and may exhibit systolic expansion on fluoroscopy.

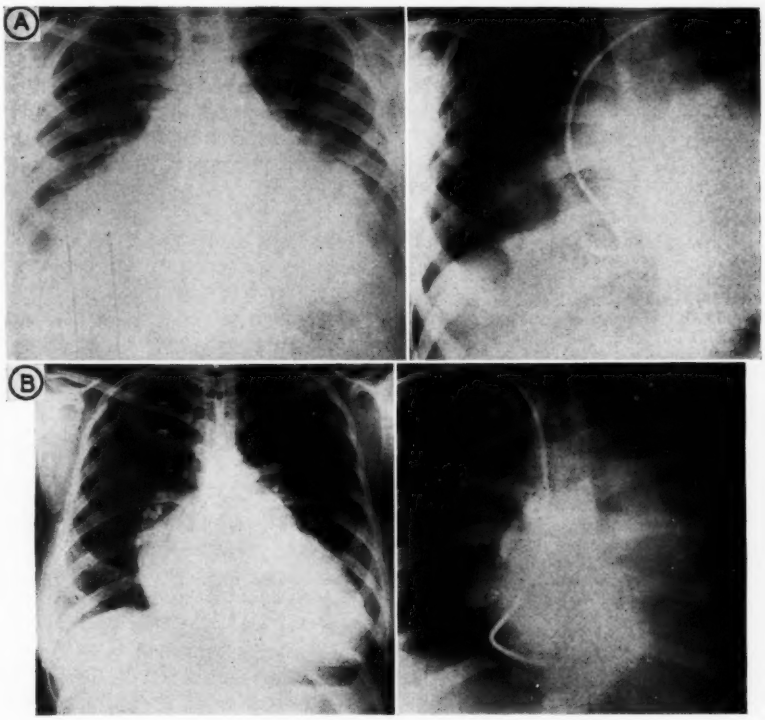

FIG. 4.—Contrast in catheter findings between (A) pericardial effusion, and (B) aneurysmal left atrium.

SUMMARY AND CONCLUSION

The radiological signs in 23 episodes of rheumatic pericardial effusion have been investigated. A sudden increase of cardiothoracic ratio and straightening of the left border were the most consistent and the earliest signs of developing effusion. Change of contour, bulging of the right border, widening of the vascular pedicle, disappearance of the shadow of the descending aorta,

and haziness of the posterior border in the oblique view were less consistent and usually later signs, but nevertheless useful ones. No constant change in the right cardio-diaphragmatic angle was observed.

A diminution in cardiothoracic ratio was the earliest radiological sign of resolution. Narrowing of the vascular pedicle, increased clarity of the posterior border in the oblique view, and return to normal of the right border followed later. Straightening of the left border and absence of the shadow of the descending aorta persisted longest, in some cases indefinitely.

The effect of posture on the shape of the heart shadow in pericardial effusion has been studied, particularly that of tilting head downwards to elicit the sign of divergent vascular shadows. This sign was found to be of limited value in the differentiation between effusion and cardiac enlargement.

Cases that had been diagnosed as having cardiac enlargement from established valve lesions were reviewed, and six of them were diagnosed in retrospect as having had effusions. Points that were of value in making this distinction are emphasized.

Cases with carditis have been reviewed to determine the incidence of rapidly progressive cardiac enlargement in the absence of pericarditis. It occurred in only 9 out of 215 cases; all of them had established valve lesions and active rheumatism, and one had failure. Only in the one with failure was the rate of increase comparable to that which had been observed in pericardial effusion. Acute dilatation does not, therefore, seem to occur in early rheumatic carditis.

Seventeen cases with and without effusion have been catheterized. The value of the technique in differentiating between pericardial effusion and cardiac enlargement is emphasized.

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THE INCIDENCE AND LIFE EXPECTATION OF CHILDREN WITH CONGENITAL HEART DISEASE

BY

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From the Department of Social Medicine, University of Birmingham

Received August 12, 1952

An acceptable estimate of the incidence of congenital heart disease in the general population of births is not yet available. Observations recorded at birth on series of consecutive births have given figures that are clearly much too low, which is scarcely surprising in view of the uncertainty of diagnosis in the newborn. Malpas (1937) found only 10 patients with heart defects among 13,964 births (0·7 per thousand) and DePorte and Parkhurst (1945) noted 142 in 300,795 births (0·5 per thousand). Estimates of incidence in patients examined post mortem (reported by Leech, 1935; and Potter, 1940; among many others) or in patients admitted to hospitals (Roberts, 1937; Thordarson, 1947) vary widely, and are equally unsatisfactory as indices of incidence in all births. Perhaps the most reliable data have been derived from examination of school children, for whom Sampson *et al.* (1938), Rauh (1939) and Weiss (1941) gave estimates between 0·14 and 0·16 per thousand. These figures are of course unacceptable as an expression of incidence in the general population of births. Data recorded in the Registrar-General's Statistical Review of England and Wales indicate that the majority of deaths attributed to congenital heart disease occur before the end of the first year of life, and even when allowance is made for errors in certification it can hardly be doubted that early mortality is very high.

There is no reliable information about the life expectation at birth of affected children. Survival rates have, however, been examined for selected individuals who survived for some time after birth, for example by Ash and Harshaw (1939) for grouped cardiac malformations, and by Benn (1947) for patent ductus arteriosus.

In the present communication we record estimates of incidence and life expectation at birth based on all cases of congenital heart disease (633) identified at birth or later in a population of 199,418 total births. The main sources of error are (*a*) erroneous certification of cause of death in children who died without post-mortem examination or adequate clinical investigation, and (*b*) incomplete recording of children with minor malformations who survived. Reasons are given for believing that these errors are unlikely to prejudice seriously the reliability of the estimates.

Materials. We have attempted to obtain information about all cases of congential heart disease born in the years 1940–49 to mothers domiciled within the administrative boundary of Birmingham. Data were collected from the following sources.

(1) Records of all post-mortem examinations conducted in maternity, pædiatric, and general hospitals in the city.

(2) Clinical records of all patients seen by consultant physicians or surgeons in the same hospitals.

(3) Records of all patients attending special schools or under the supervision of school medical officers in ordinary schools.

(4) Local Authority registers of stillbirths and neonatal and infant deaths.

There were 633 cases which are classified in Table I according to the method of diagnosis.

* In receipt of a grant from the Medical Research Council.

TABLE I

METHOD OF DIAGNOSIS OF CONGENITAL HEART DISEASE IN 633 PATIENTS BORN IN BIRMINGHAM, 1940–49

Diagnosis	Number of cases	Percentage of total
Post mortem	236	37·3
At operation for patent ductus arteriosus ..	19	3·0
By consultant physician	223	35·2
By school medical officer	10	1·6
From death register	145	22·9
Total	633	100·0

The method of diagnosis is the most reliable of the alternatives available: for example, of 63 patients reported by school medical officers, 47 are shown under " by consultant physician," and 6 under " by operation for patent ductus arteriosus "; and of 355 cases in Local Authority infant death registers, 210 were confirmed by an alternative and more reliable source of information. Of the 223 cases in which the diagnosis rested on the opinion of a consultant 168 (75%) were seen at the Birmingham Children's Hospital. The diagnosis of the specific cardiac defect is given in Appendix A for 255 patients examined post mortem or at operation for patent ductus arteriosus, and in Appendix B for 117 of the 223 patients examined by consultants. In the remaining 106 cases seen by consultants (and not submitted to operation or post mortem) no specific diagnosis was made.

INCIDENCE

Table II gives the incidence of congenital heart disease in Birmingham (1940–49) as 3·2 per thousand total births. For the years 1940–44, when because of the longer period of observation ascertainment was more complete than in later years, incidence was 3·6 per thousand total births, and 3·7 per thousand live births. We may now consider briefly to what extent these estimates are likely to be affected by errors of observation.

(*a*) *Incidence in Stillbirths* (5 in 5202 or 1·0 per thousand). During the period of enquiry less than half of all Birmingham stillbirths were submitted to post-mortem examination, without which

TABLE II

INCIDENCE OF CONGENITAL HEART DISEASE

Year	No. of cases	Related total births	Incidence per 1000 total births
1940	55	16,424	3·4
1941	40	14,508	2·8
1942	68	18,200	3·7
1943	90	19,911	4·5
1944	78	22,285	3·5
1945	63	19,685	3·2
1946	48	22,717	2·1
1947	79	24,577	3·2
1948	52	20,999	2·5
1949	60	20,112	3·0
Total	633*	199,418†	3·17

* 5 stillbirths; 628 livebirths.
† 5202 stillbirths; 194,216 livebirths.

the diagnosis is of course quite unreliable. Incidence can be estimated from results of post-mortem examinations of consecutive stillbirths, and by combining data reported by Browne (1924), Rannels and Propst (1937), Evans and Smith (1946) and Morison (1952) we have obtained a figure of 3 per thousand (3 cases in 984 stillbirths). [A series recorded by Jacobius and Moore (1938) gives a much higher incidence (17 cases in 335 stillbirths), but we have not included it because the findings are at variance with those from other sources.] On the available evidence it seems probable that congenital malformation of the heart is not a common cause of stillbirth (Potter, 1938), and the incidence in stillbirths may be little higher than in all births. If this is the case approximately 15 malformations might have been expected among the 5202 stillbirths notified in Birmingham in the years 1940–49, which suggests that about 10 have been missed.

(*b*) *Incidence in Livebirths* (628 in 194,216, or 3·2 per thousand). There are three obvious sources of error in estimating incidence in livebirths.

(i) Deaths wrongly attributed to congenital heart disease. We can probably accept the certification of cause of death as reasonably reliable in cases submitted to necropsy (236) or examined by a consultant physician (59). It is with the diagnosis in the 145 infants recorded in the infant death register who died without adequate clinical or post-mortem examination that serious difficulty appears. All of these deaths occurred within the first year of life (93 within the first week) and it seems quite certain that in some of them cause of death was incorrectly diagnosed. Table III gives the distribution of the 145 cases according to place of birth and age at death, and strongly

TABLE III

DISTRIBUTION BY PLACE OF BIRTH AND AGE AT DEATH OF 145 UNCONFIRMED CASES RECORDED FROM THE DEATH REGISTER

Age at death	Place of birth			Total
	Hospital	At home	Nursing home or unknown	
— 3 days	4 (21)	60 (71)	4 (8)	68 (100)
— 1 week	7 (21)	16 (23)	2 (6)	25 (50)
— 1 month	4 (23)	9 (33)	7 (19)	20 (75)
— 3 months	4 (17)	8 (29)	3 (11)	15 (57)
— 1 year	5 (24)	7 (42)	5 (7)	17 (73)
Total	24 (106)	100 (198)	21 (51)	145 (355)

Numbers in brackets are the total numbers of registered deaths in which the diagnosis was confirmed or unconfirmed.

suggests that a number of deaths of children delivered at home were wrongly attributed to congenital heart disease. It seems unlikely that the incidence of affected would be higher in domiciliary than in hospital births (the incidence of congenital heart disease does not appear to be associated with maternal age or birth order, MacMahon, 1952), and, indeed, among the 212 children who died after the third day of life the proportion of hospital deliveries (40%*) is approximately the same as among 1086 controls (41%*) considered to be representative of all births in the city. But of the 92 children who died within the first three days, 71 were delivered at home, which is roughly 40 in excess of the number expected (31) assuming the relative proportions of domiciliary and hospital births to be the same in children who died before and after three days. In 60 of the 71 cases the diagnosis was unconfirmed. It is of course possible that children with congenital heart disease receive less effective treatment and consequently die earlier if born at home, but it seems much

* These estimates are based on the total number of births in hospital or at home, which excludes births in nursing homes, or for which place of delivery was unknown.

more likely that the high incidence of early domiciliary deaths from this cause is explained by errors in diagnosis.

If, therefore, we accept the incidence of first-year deaths in hospital births (of which the majority were confirmed post mortem) as reasonably reliable and assume that the incidence is roughly the same in domiciliary as in hospital births, the data suggest that the number of registered deaths is about 40 more than it should be. These 40 will be included among the 100 domiciliary births in which the diagnosis was unconfirmed.

(ii) Omission of patients who died without recognition of a congenital heart lesion. There is no means of assessing the number of cases lost in this way, but it seems unlikely that it is large.

(iii) Omission of patients who had not come to medical attention at the time of enquiry. We have no information about the incidence of cardiac malformations in children who survived more than 11 years without coming to medical attention. Moreover, for most of the 633 cases the length of the history is much less than 11 years, and for children born in 1949 it is less than 3 years (the enquiry was completed in January, 1952). By using the data available for the earlier years to give an expected incidence in the later years an estimate has been made of the number of cases lost because the histories were less than 11 years. Forty-two affected appear to have been lost for this reason.

To sum up: examination of the data upon which the estimate of incidence of congenital heart disease is based suggests that approximately: (*a*) 10 stillborn affected have been missed; (*b*) 40 first-year deaths were wrongly attributed to congenital heart disease; and (*c*) 42 more affected children would have been discovered if an 11-year history had been available in all cases. No estimate is made of numbers of deaths of affected not attributed to congenital heart disease; and patients who left the area or who reached the age of 11 without being identified. On the whole it seems probable that the estimated incidence (3·2 per thousand total births) slightly understates the true incidence.

SURVIVAL

Table IV gives estimated death rates according to age, based on 628 liveborn children with congenital heart disease. The method of estimation is as follows. From the number of patients known to be alive at the beginning of each period (column 1) is subtracted the number lost (column 2) for reasons other than death during that period (for example patients lost sight of, or patients who had not reached the end of the age interval under consideration at the time of enquiry). The number subtracted is corrected for that proportion of the interval for which each patient's history is incomplete; this gives the number at risk of death during the age interval (column 3)

TABLE IV

ESTIMATED DEATH RATES ACCORDING TO AGE OF LIVEBORN CHILDREN WITH CONGENITAL HEART DISEASE

Age period	1 Number known to be alive at beginning of each period	2 Number lost for reasons other than death	3 Number at risk of death	4 Number of deaths	5 Death rate (per cent)
Birth —	628	0	628	54	8·6
1 day — ..	574	0	574	130	22·6
1 week — ..	444	0	444	72	16·2
1 month — ..	372	2	371	73	19·7
3 months — ..	297	1	296	52	17·6
6 months — ..	244	4	241	42	17·5
1 year — ..	198	55	171	8	4·7
5–9 years ..	135	106	74	9	12·1

NOTE:—The method of calculation is described in the text.

of which the number of deaths during the interval (column 4) is expressed as a proportion (column 5). The death rates recorded in column 5 are somewhat irregular, but it must be remembered that the age intervals examined are of different lengths.

The age specific death rates from Table IV are used in Table V to give in life table form the estimated numbers of 1000 liveborn infants with congenital heart disease surviving to ages up to 10 years (shown in column 3). Of 1000 children alive at birth, 86 would be expected to die during the first day, leaving 914 alive at one day, of whom 207 would die during the remainder of the first week. Numbers alive at 1 month, 6 months, 1 year, and 10 years are 592, 391, 323, and 271 respectively.

We may now enquire to what extent these estimates are affected by the errors referred to above. Life expectation has been recalculated after (*a*) removal of 40 from the number of deaths under one week, and (*b*) addition of 42 to the number of children surviving to age 10 years (column 4).

TABLE V

ESTIMATED SURVIVAL RATES OF 1000 LIVEBORN INFANTS WITH CONGENITAL HEART DISEASE

Age period	Probability of dying during each period (1)	Number of deaths during each period (2)	Number alive at beginning of each period		Estimate* of incidence per (thousand) in the related population at beginning of each period (5)
			Not adjusted (3)	Adjusted* (4)	
Birth —	0·086	86	1000	1000	3·2
1 day —	0·226	207	914	946	3·0
1 week —	0·162	115	707	771	2·5
1 month —	0·197	117	592	657	2·1
3 months — ..	0·176	84	475	541	1·8
6 months — ..	0·175	68	391	458	1·5
1 year —	0·047	15	323	390	1·3
5 years —	0·121	37	308	375	1·2
10 years	—	—	271	346	1·1

* See text for description of the method of adjustment.

These changes were of course suggested by the considerations discussed earlier in the examination of incidence. The data suggest that of 10 affected children born alive, 2 die by the end of the first week, between 3 and 4 by the end of the first month, and 6 by the end of the first year. Between 3 and 4 survive to the tenth birthday.

The adjusted survival rates have been used to calculate the incidence of children with congenital heart disease, which is expressed per 1000 children alive at the beginning of each period (column 5). For example, of 1000 children alive at birth, 3·2 are affected, as compared with 1·1 per 1000 children alive at 10 years. No allowance has been made for reduction in the related population because of deaths due to other causes, but the error that results is small.

ASSOCIATED MALFORMATIONS

In the present context we may consider briefly the frequency of association between malformation of the heart and other congenital malformations. For this purpose we have excluded the 145 cases recorded from the death register, for which data are incomplete. Table VI gives details of other malformations observed in 101 (21%) of the remaining 488 subjects. The commonest association is with mongolism, which was exhibited by 31 (6%) of the 488 cases. The nature of the heart lesion was known in 18 (of the 31); 14 were septal defects. The association of mongolism with atrial and ventricular septal defects was previously noted by Abbott (1927) and Silvy (1933).

Except in the case of mongolism there is no noteworthy association with any other single

malformation. Nevertheless, the incidence of other defects, for example of the central nervous system or alimentary tract, is of course much higher in children with congenital heart disease than in the general population of births.

TABLE VI

MALFORMATIONS ASSOCIATED WITH CONGENITAL MALFORMATIONS OF THE HEART

Cardiac malformation	Associated malformation						Number with associated malformations	Number without associated malformations	Total
	Mongolism	Central nervous system and special senses	Alimentary tract	Skeletal	Genito-urinary	Other			
Transposition of great vessels ..	—	—	2	1 (1)	— (2)	—	3	44	47
Persistent common arterial trunk ..	—	1	3	1 (1)	— (1)	1	6	11	17
Pulmonary stenosis ..	—	1	2 (1)	2	2 (1)	1	8	34	42
Coarctation of aorta	—	—	1	— (1)	3	1 (1)	5	27	32
Septal defects ..	14	3	4 (4)	5 (2)	5 (3)	3 (2)	34	87	121
Patent ductus arteriosus	1	2	—	— (2)	1	2	6	56	62
Other specified defects	3	— (1)	6	— (2)	— (1)	5 (4)	14	37	51
Defects not specified	13	3	3 (1)	5 (2)	—	1	25	91	116
Total ..	31	10 (1)	21 (6)	14 (11)	11 (8)	14 (7)	101	387	488

In brackets are the numbers of individuals exhibiting a particular associated malformation who have been classified under other associated abnormalities.

SEX RATIO

Of the 633 patients 338 (53%) were males. The numbers of each sex are recorded in Appendices A and B according to type, and sex ratios (expressed as the percentage of males) are given for the main groups in Table VII. For this purpose we have combined patients diagnosed post mortem and by consultant examination, since sex ratios of cases confirmed by the two methods are fairly consistent. The results are compared with those of Abbott (1936). Except in the case of patent ductus arteriosus, sex ratios for the various classes of malformation are different in the two series; but it must be remembered that numbers are rather small, and that Abbott's material can by no means be regarded as representative.

Sex ratios slightly above 50 have generally been reported in series of grouped congenital heart defects, for example by Leech (1935), Abbott (1936), Roberts (1937), Gibson and Clifton (1938), Ash and Harshaw (1939), Rauh (1939), and Campbell (1949). Brown (1939) reported 300 cases among which there was a slight excess of females.

SUMMARY

An attempt has been made to obtain information about all cases of congenital heart disease born to Birmingham mothers in the years 1940–49. In a population of 194,418 total births 633

TABLE VII

SEX RATIOS FOR SPECIFIC CARDIAC MALFORMATIONS

Malformation	Birmingham 1940–49		Date recorded by Abbott (1936)	
	Number of cases	Percentage of males	Number of cases	Percentage of males
Transposition of great vessels	47	72	81	52
Persistent common truncus arteriosus	17	47	21	52
Pulmonary stenosis	42	69	150	50
Coarctation of aorta	32	44	87	71
Septal defects	121	55	122	46
Patent ductus arteriosus	62	39	105	34

affected were identified. Diagnosis was confirmed at necropsy (236) or operation for patent ductus arteriosus (19) or by a consultant physician (223). In the remainder the diagnosis depended upon the report of the school medical officer (10) or certification of cause of death (145).

Incidence during the whole period was 3·17 per thousand total births, and 3·23 per thousand live births. For the years 1940–44, when ascertainment was more complete than in later years, incidence was 3·62 per thousand total births and 3·73 per thousand live births.

Estimates of life expectation at birth suggest that of 10 affected children born alive, 2 die by the end of the first week, between 3 and 4 by the end of the first month, and 6 by the end of the first year. Between 3 and 4 survive to the tenth birthday.

Associated abnormalities were observed in 101 (21%) of 488 cases. Thirty-one were mongols. Of 18 mongols in which the nature of the heart lesion was known, 14 had septal defects. There was no noteworthy association between congenital heart disease and any other single malformation.

Sex ratios are recorded for various types of malformation.

For facilities in the collection of case records, we are indebted to the following: (1) The staff of the Birmingham Children's Hospital, in particular Dr. Clifford Parsons who made available the records of the congenital heart clinic; (2) The staffs of all other Birmingham hospitals, in particular of Selly Oak and Dudley Road Hospitals; (3) Dr. H. S. Baar, Dr. W. Whitelaw, and other hospital pathologists for access to post-mortem material; (4) Dr. H. M. Cohen, Dr. M. E. Lemin, and their assistant school medical officers for organizing and executing an inquiry into the numbers of cases of congenital heart disease among school children; (5) Dr. Jean Mackintosh and the staff of the Maternity and Child Welfare Department for free access to departmental records.

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APPENDIX A

DIAGNOSIS IN 255 PATIENTS EXAMINED POST MORTEM OR AT OPERATION FOR PATENT DUCTUS ARTERIOSUS

	M	*F*	*Total*
1. *Transposition of Great Vessels*			
(*a*) with ventricular septel defect[1]	6	4	10
(*b*) with cor triloculare[2]	1	1	2
(*c*) with no ventricular septal defect[3]	8	1	9
(*d*) state of septum unknown	6	1	7
(*e*) right-sided aorta with ventricular septal defect	2	1	3
(*f*) dextroposition of aorta with ventricular septal defect	3	—	3
(*g*) various[4]	3	1	4
	29	9	38
2. *Persistent Common Truncus Arteriosus*			
(*a*) with cor biloculare (3) or single ventricle (1)	3	1	4
(*b*) from left ventricle with ventricular septal defect	1	4	5
(*c*) from right ventricle with septal defect and rudimentary left ventricle[5]	4	3	7
	8	8	16
3. *Pulmonary Stenosis*			
(*a*) with ventricular septal defect (3)[6] or single ventricle (2)	2	3	5
(*b*) Fallot's tetralogy	6	1	7
(*c*) with no ventricular septal defect	4	—	4
(*d*) with other lesions[7]	3	2	5
	15	6	21
4. *Coarctation of Aorta*			
(*a*) with patent ductus arteriosus[8]	4	6	10
(*b*) with single ventricle and hypoplasia left heart	2	1	3
(*c*) complete atresia (8) or non-development (6) of arch of aorta	4	10	14
	10	17	27
5. *Septal Defects*			
(*a*) atrial septal defect[9]	12	10	22
(*b*) ventricular septal defect[10]	14	15	29
(*c*) atrial and ventricular septal defects[11]	6	4	10
(*d*) cor triloculare	1	3	4
(*e*) cor biloculare	4	—	4
	37	32	69
6. *Patent Ductus Arteriosus*			
(*a*) diagnosed at operation[12]	4	15	19
(*b*) diagnosed post mortem[13]	14	12	26
	18	27	45
7. *Other defects*			
(*a*) patent foramen ovale	10	1	11
(*b*) idiopathic cardiac hypertrophy	4	2	6
(*c*) dextrocardia[14]	2	1	3
(*d*) hypoplasia of aorta and left ventricle[15]	3	3	6
(*e*) hypoplasia of left ventricle[16]	2	1	3
(*f*) aortic[17] (1), mitral[18] (3), tricuspid[19] (1), or combined (2) valvular stenosis	6	1	7
(*g*) fœtal endocarditis[20]	2	—	2
(*h*) pulmonary veins opening into separate chamber—no connection with auricles or ventricles	—	1	1
	29	10	39

Notes to Appendix A

1 One with tricuspid atresia; one with single atrium; one with atrial septal defect and atresia of aorta between 4th and 6th left arches.
2 One with atrial septal defect.
3 One with slight coarctation of aorta.
4 One with over-riding aorta, pulmonary artery from left ventricle and pulmonary stenosis; one with complete transposition with descending aorta from pulmonary artery through patent ductus (i.e. from left ventricle); one with aorta from right ventricle and absent pulmonary artery; one with cor biloculare and pulmonary stenosis.
5 One with absent arch of aorta.
6 One with bicuspid aortic valves.
7 One with reduplication of pulmonary artery; one with hypoplasia of right heart; three with endocarditis.
8 One with biscuspid aortic valve.
9 Four with widely patent ductus arteriosus.
10 One with malformation of pulmonary and mitral valves; one with tricuspid fœtal endocarditis; one with hypoplasia of aorta; one with " absent pulmonary valves "; one with hypoplasia of LV. and biscuspid aortic valve.
11 Three with malformation of tricuspid or mitral valve; one with hypoplasia of aorta.
12 Two with suspected additional lesions.
13 Seven with widely patent foramen ovale.
14 One with cor triloculare and VSD; one with cor biloculare and hypoplasia of pulmonary artery.
15 Two with fœtal endocarditis.
16 One with transverse septum in left atrium; one with absent right pulmonary vessels.
17 With bicuspid aortic valve.
18 One with atrial and ventricular septal defects.
19 With rudimentary left atrium.
20 One with bicuspid aortic and pulmonary valves.

Appendix B

Provisional Diagnosis in 117 of 223 Patients examined by Consultants

	*Full investigation**	*Partial investigation†*	*M*	*F*	*Total*
1. Transposition of great vessels					
(*a*) complete transposition	1	2	2	1	3
(*b*) Eisenmenger's complex	—	6	3	3	6
2. Persistent common arterial trunk	1	—	—	1	1
3. Pulmonary stenosis					
(*a*) Tetralogy of Fallot	12	5	12	5	17
(*b*) Pulmonary stenosis	1	3	2	2	4
4. Coarctation of aorta	2	3	4	1	5
5. Septal defects					
(*a*) Atrial septal defect	—	7	3	4	7
(*b*) Ventricular septal defect	1	41	25	17	42
(*c*) Not specified or combined defects	1	2	2	1	3
6. Patent ductus arteriosus					
(*a*) Alone	—	14	5	9	14
(*b*) With other defects	—	3	1	2	3
7. Other defects					
(*a*) Dextrocardia[1]	4	—	1	3	4
(*b*) Heart block[2]	5	—	5	—	5
(*c*) Sub-aortic stenosis	—	3	2	1	3
Total	28	89	67	50	117

[1] Two with other defects
[2] Four with other defects.

* Includes angiogram and cardiac catheterization where appropriate.
† Includes X-ray and electrocardiogram.

A MULTI-CHANNEL CATHODE-RAY PHONOCARDIOGRAPH

BY

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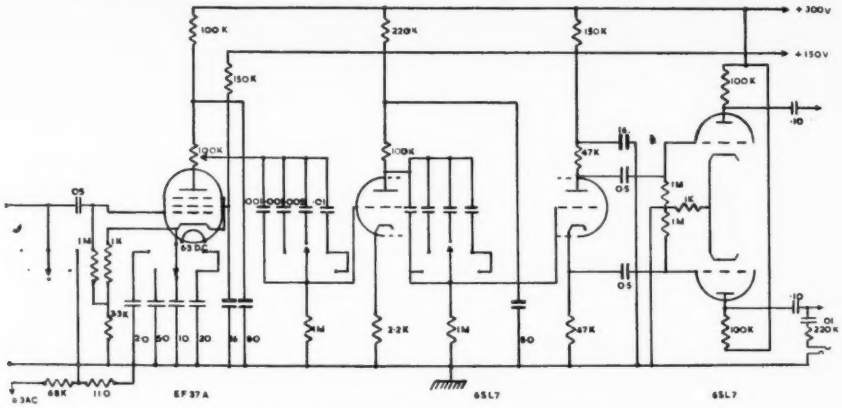
The difficulties of recording the faint murmurs of early rheumatic valvulitis are well known, and for this reason it was considered advisable to develop a cathode-ray phonocardiograph. This is theoretically the ideal recording device owing to its minimal inertia and high sensitivity. This phonocardiograph is intended to provide objective confirmation of clinical findings on auscultation, recording change in murmurs during rheumatic activity and convalescence and at subsequent examinations. The patients, mainly children, are admitted to hospital shortly after the onset of rheumatic fever, and are not discharged until convalescence is completed.

The ear is more sensitive to sounds of high frequency than to those of low frequency, and although the actual intensity of the low-pitched heart sounds is far greater than that of high-frequency murmurs, the logarithmic low-frequency attenuation of the ear may cause them to sound equally loud. For this reason, filtering of the low-frequency sounds must be employed in order to record the murmurs satisfactorily. Mechanical filtering is employed in routine clinical auscultation by the use of the stethoscope bell or diaphragm. Rappaport and Sprague (1941, 1942) employ similar methods to record linear, stethoscopic, or logarithmic phonocardiograms. The first of these corresponds to the apex cardiogram without filtration, and the latter two filter the lower frequencies in increasing degree, so that the logarithmic record is equivalent to the auscultatory findings. In this country more stress has been laid on electrical methods of sound filtration (Leatham, 1949, and Cowen and Parnum, 1949), by attenuation of the lower and amplification of the higher frequencies. Various numbers of filters are employed by different workers, and we use four. The two low-pass filter positions are used for recording heart sounds and mitral diastolic murmurs, whereas the high-pass filter position (with maximal attenuation of low-pitch sounds) is best for recording aortic diastolic murmurs. The over-all gains on these amplifiers are 104 db. on the low-frequency, and 101 db. on the high-frequency positions at 500 c./s.

DESCRIPTION

Microphone. A crystal microphone was selected owing to its high sensitivity, small size, and high signal-to-noise ratio. We use an Acos model (type MIC. 14–3) which has an almost flat response curve in the frequencies 30 c./s. to 1000 c./s. The microphone is mounted in an ebonite holder which is attached to the chest by suction, the negative pressure being applied through a grooved lip, and not to the bell of the holder. An air-pressure equalizing valve maintains normal atmospheric pressure within the bell when this is applied to the chest and prevents damage to the diaphragm and crystal. This suction attachment of the microphone to the chest is preferable to the use of glue or straps, as it does not cause any noise between the case and the chest wall; and as the pressure of attachment is constant, comparable serial recordings are obtained. The microphones are connected to the amplifiers by coaxial cable.

The phonocardiograph amplifier (Fig. 1) consists of a low-microphone pentode followed by a double triode, the first section of which operates as an amplifier and the second as a phase splitter. The balanced output of the phase splitter feeds the output double triode, providing a balanced output voltage for the cathode-ray tube. Variable base-cut response control is provided by the switched cathode capacitors in the first valve and the coupling capacitors between first and second, and second and third stages. The heater


+300v
+150v
100K
150K
220K
150K
100K
120K
100K
47K
1M
1K
.05
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at the same level of gain as that being employed for phonocardiography. Thus calibration of amplification is available, and is of value in assessing the changing intensity of murmurs over a period of time. Of course for this purpose the microphone must be applied at the same site on each occasion and the patient must be lying in the same position. Recordings are routinely made with the patient holding his breath in expiration. Provision for a headphone attachment is made in order that auditory " monitoring " may be employed.

A stabilized power supply provides H.T. for the amplifier. The cathode-ray tube is an electrostatic deflection tube with a blue screen of $1\frac{1}{4}$ in. diameter, suitable for photography.

The electrocardiographic amplifier (Fig. 3) employs balanced stages, each consisting of a double triode valve. Long-tail-pair connections are used for the first two stages to provide coupling between the two halves and ensure a balanced output to the cathode-ray tube for balanced, unbalanced or differential input signals. The heaters of the valves are supplied as in the phonocardiograph amplifier. The electrocardiogram is routinely recorded by standard lead two. Alternatively, this amplifier may be used for recording the jugular phlebogram. A short rod of balsa-wood is connected to the diaphragm of a crystal micro-

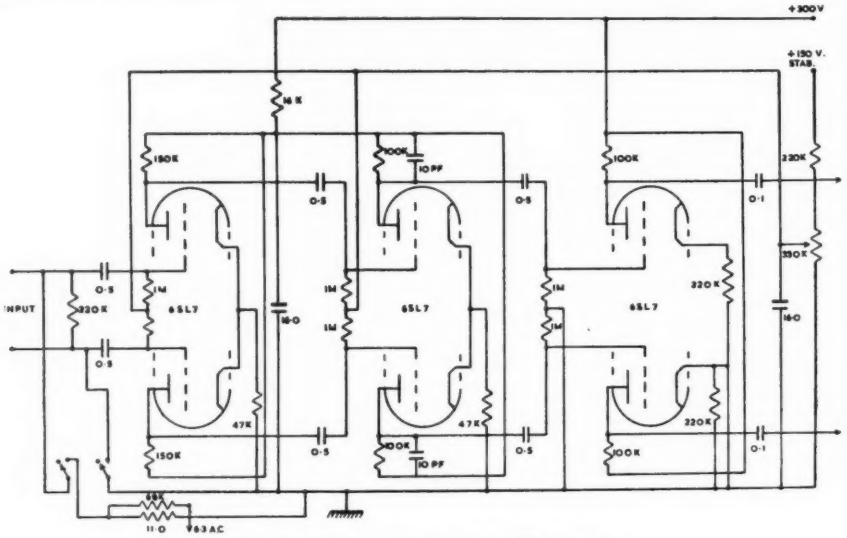

FIG. 3.—Electrocardiograph amplifier circuit.

phone and is used as the " pick-up " of the venous pulse. This microphone is then connected to the amplifier through the necessary resistance and capacitance to provide a suitable time-constant.

In the present machine four phonocardiograph and two electrocardiograph amplifiers are provided. In practice, however, it is only suitable for use on four channels, 3 phono-, 1 electro-cardiographic, which are quite adequate for routine use. These six amplifiers with C.R.O. tubes and the power unit form the lower part of the apparatus; the photographic unit being placed directly above.

The six cathode-ray tubes face forwards and the screens can be readily observed. Controls for brilliance and focus are provided. For recording, a hinged plane mirror is brought down before the cathode-ray tubes, forming an angle of approximately 45° with the screens. This mirror reflects the cathode-ray images upwards and backwards to a concave mirror; from here the images converge on to the photographic paper. This paper is driven from the loading to the receiving cassette at a speed of 75 mm./sec. Gearing is provided for altering this speed if required. A time marker records 1/10 sec. intervals at the edges of the paper. 100 ft. spools of Ilford recording papers, 120 mm. width (B.P.I.) are used. The switch operating the motor drive simultaneously opens the shutter of the camera, making it impossible to operate the camera motor with the shutter closed. The complete equipment measures 36 in. high and 19 in. wide and is suitable for standard rack mounting.

USE

In practice two microphones are used simultaneously, one at the base and one at the apex. The basal murmurs are usually recorded at the high-pass filter position in order to accentuate the

high-pitched aortic diastolic murmurs. The apical microphone is connected to two leads, so that if required, simultaneous apical records may be taken at high and low-pass filter positions on the remaining two phonocardiograph amplifiers. Thus high-frequency apical systolic and low-frequency mitral diastolic murmurs and heart sounds are recorded synchronously. The fourth amplifier records either electrocardiogram or phlebogram, as desired.

In order to reduce interference from outside noise a sound-proof room was constructed for these recordings. A small brick building, 14×12×11 ft. attached to the main building on only one wall was selected. The window was blocked and double doors inserted. Within this building an inner room, 6½×8×8 ft. was constructed, with a 6 in. concrete base, resting on coarse fibre-glass which insulates it from the main structure. The walls are of brick and the roof of 6 in. concrete, one door being the only opening. The interior is lined with fibre-glass and perforated hard-board to prevent internal reflection of noise. Thus the inner room is isolated from all direct sources of noise conduction from the main building. The patient lies on a couch in this room, and the recording machine is in the outer room in order to eliminate transmission of noise from the camera motor to the microphones. A light signalling system provides communication between the attendant with the patient and the person operating the phonocardiograph. The outer room is used also as a dark room for immediate processing of the photographic paper.

In order to check the alignment of the traces on the four tubes, a common signal is injected, and any asynchrony is apparent when checking the photographic record with a set-square. A control on each amplifier allows adjustment of the X-shift to obtain correct alignment.

This machine has now been in routine use for one year, during which time numerous phonocardiograms have been obtained from 170 patients of all ages. As it is quite simple to expose many feet of paper during one recording, it is almost always possible to select a satisfactory tracing from even the most uncooperative patients. The principal difficulties arise from respiration and from chest muscle noises and in some cases recordings have to be taken during quiet respiration. Satisfactory photographic reproduction depends upon the brilliancy of the cathode-ray " spot " and on the extent and the frequency of its excursion. Thus a high-pitched, loud systolic murmur will appear less well defined than a mitral diastolic murmur of low-frequency and amplitude. In addition, satisfactory photographic development is essential if a good tracing is to be obtained. Examples of two phonocardiograms are shown in Fig. 4 A and B.

FIG. 4 A.—Systolic murmur and aortic diastolic murmur.

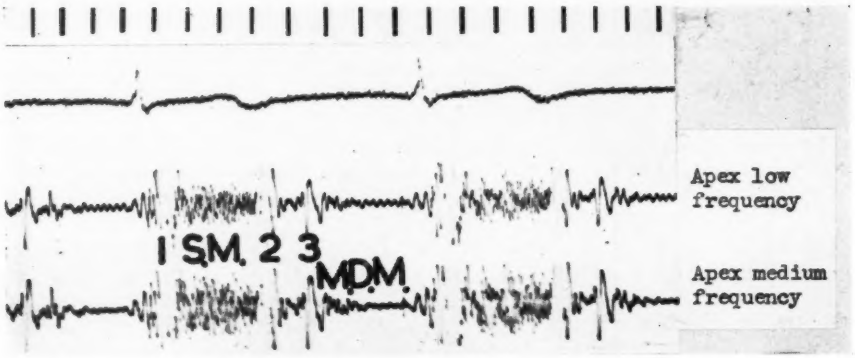

FIG. 4 B.—Mitral systolic and diastolic murmurs.

SUMMARY

A new multi-channel cathode-ray oscillograph phonocardiograph is described. This machine has been devised in order to study the murmurs of rheumatic carditis, and satisfactory recordings have been obtained of the faint diastolic murmurs frequently found in the early course of rheumatic activity.

This work was initiated at the suggestion of Dr. P. Wood, Dr. E. G. L. Bywaters, and Dr. G. T. Thomas, to whom we are extremely grateful. In addition, we are indebted to Mr. R. B. Archbold of the G.P.O. Research Station, Dr. L. Bernstein, and Dr. A. Leatham for much valuable technical advice. Dr. J. C. Simmonds and Dr. J. E. Varrall of Airmec Laboratories Ltd. undertook the final design and construction of this apparatus.

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THE OPENING SNAP OF MITRAL STENOSIS

BY

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Sixteen years after Laennec (1819) described the murmur of mitral stenosis, Bouillaud (1835) described a reduplication of the second sound in mitral stenosis. The familiar cadence in mitral stenosis, which results from the presence of this added sound, was likened by Durozier (1862) to the syllables ffou-ta-ta-rou. In 1872 Guttman suggested that this sound might be due not to asynchronism of pulmonary and aortic valve closure, as had been held by Durozier, but to vibration at the stenosed mitral valve itself. Sansom (1881) held the same views as Guttman. It was not until 1888 that Rouchès introduced the term commonly used today " claquement d'ouverture de la mitrale " or opening snap of the mitral valve, to describe this sound, stating that Potain had used this term in his teaching. He suggested that the sound was produced by sudden stretching of the stenosed mitral valve by blood passing from the left auricle to the left ventricle. Rouchès' views on the pathogenesis of the opening snap were not universally accepted and Gallavardin (1905) and Duchosal (1946) postulated other mechanisms. Margolies and Wolferth (1932) made a detailed clinical and phonocardiographic study of this sound and concluded that Rouchès' hypothesis as to its mode of production was the most likely.

The clinical recognition of the opening snap and its differentiation from two other sounds in early diastole, may sometimes present difficulty. The second component of the second sound when widely split may closely resemble an opening snap. Further, the physiological third heart sound might be confused with the opening snap. The heart sounds were examined clinically and in the phonocardiogram in 33 cases of mitral stenosis to test certain clinical signs that might make easier the differentiation and recognition of these sounds.

The Investigation Described

Mitral stenosis was considered to be the principal lesion in all cases and the sole valvular lesion in 28 of them, while in four there was slight aortic incompetence and in another associated mitral incompetence. The ages of the patients varied between 19 and 48, with an average of 34 years. There were 7 men and 26 women. None had gross cardiac enlargement. The electrocardiogram showed evidence of right ventricular preponderance in 24, and auricular fibrillation was present in 12 patients. Fifteen have since had a mitral valvotomy.

Phonocardiograms were recorded on a four-channel phonocardiograph using crystal microphones, as described by Leatham (1949). An electrocardiogram was used as a reference tracing.

Incidence and Relationship of the Opening Snap

An opening snap was diagnosed clinically and confirmed on the phonocardiogram in 28 out of the 33 patients. In four of the remaining five the phonocardiogram recorded an opening snap. In three of these the sound was very soft and therefore difficult to recognize with certainty clinically ; in the fourth it followed closely the second heart sound and phonocardiography was necessary to analyse correctly the sequence of sounds. In only one case was an opening snap absent on the phonocardiogram.

The term snap well described the *quality* of the sound heard. On the phonocardiogram the sound was composed chiefly of high frequency vibrations of short duration (0·005 to 0·01 sec.).

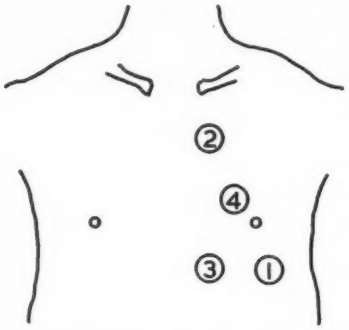

FIG. 1.—Diagram to illustrate microphone positions. (1) Mitral area. (2) Pulmonary area. (3) Left sternal edge. (4) Supramammary area.

The area where the sound was best heard was determined by examining its intensity, both on auscultation and on the phonocardiogram in four selected areas, the mitral area, the pulmonary area, the left sternal edge at the level of the fifth intercostal space, and the special supramammary area, which lies above and a little internal to the left nipple (Fig. 1). The opening snap was best heard in the supramammary area, in 27 out of 32 cases. Maximum audibility, however, was shared between two or more areas in the majority, the commonest after the supramammary area being the left sternal edge and the mitral area, and the least common the pulmonary area.

The *interval* between the beginning of the second sound and the opening snap varied widely. The minimum interval was 0·03 sec., the maximum 0·14 sec., and the average for the group 0·07 sec. (Fig. 2).

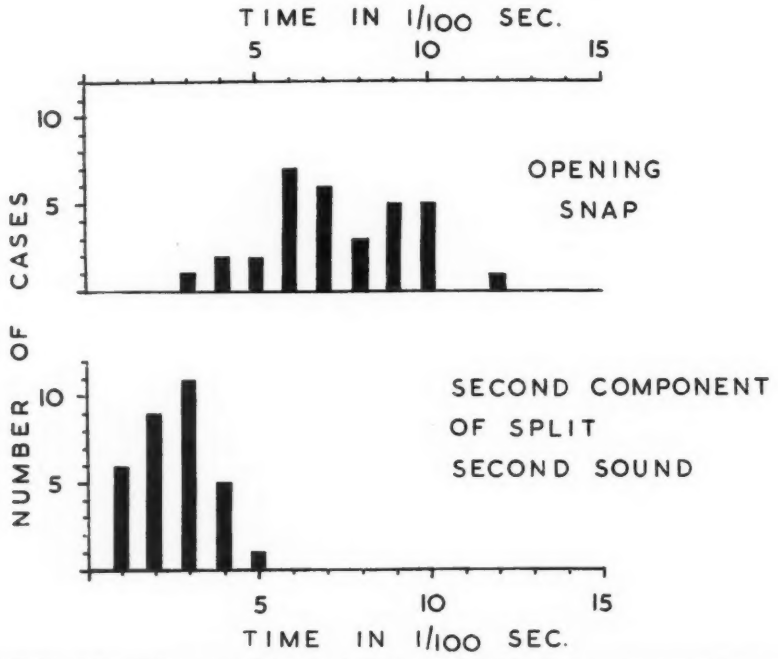

FIG. 2.—*The timing of the opening snap and the second component of a split second sound compared in* 33 *cases of mitral stenosis.* The interval between the beginning of the second sound and the opening snap varied between 0·03 and 0·12 sec. (average 0·07 sec.): that between the beginning or first component of the second sound and the second component varied between 0·01 and 0·05 sec. (average 0·03 sec.). Minimum intervals for the opening snap and maximum intervals for the second component of a split second sound lay in the same range (0·03 to 0·05 sec.). (The maximum interval between the beginning of the second sound and the opening snap (0·14 sec.) mentioned in the text, is not recorded in the Table, where only mean intervals for individual patients are shown.)

In the phonocardiogram a relationship was noted between the diastolic interval on the one hand and the interval between the beginning of the second sound and the opening snap on the other in individual patients in sinus rhythm. An increase in the diastolic interval with slowing of the heart rate was accompanied by a longer interval between the beginning of the second sound and the opening snap. No similar direct correlation was seen between these two variables in the group as a whole. In individual patients with auricular fibrillation, a general relationship was noted between the preceding diastolic interval and the timing of the opening snap that followed, the snap occurring earlier after a short and later after a long diastolic interval (Fig. 3). As in those in sinus rhythm this relationship, which held generally in most subjects, did not hold for the group as a whole, where no direct correlation was noted between the diastolic interval and the timing of the opening snap.

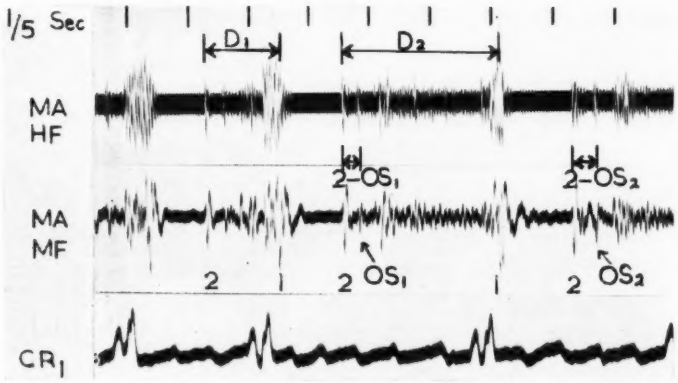

FIG. 3.—Relationship between the diastolic interval (D) and the interval between the beginning of the second sound and the opening snap (2–OS) in mitral stenosis with auricular fibrillation. A short diastolic interval (D_1) is followed by an earlier opening snap (OS_1): a longer diastolic interval (D_2) by a later opening snap (OS_2). MA=mitral area. HF and MF=high- and medium-frequency filters. CR=electrocardiographic lead CR_1.

Relationship to the Mid-Diastolic Murmur. In 27 out of 32 cases, the opening snap was closely followed by the mid-diastolic murmur on the phonocardiogram (Fig. 4). In two of the remainder a silent gap was recorded between the opening snap and the murmur (Fig. 5). In three, records did not give clear information about the time of the start of the murmur. In eight cases there was an initial crescendo to the murmur, which reached its greatest intensity about 0·05 sec. after the opening snap (Fig. 4). Clinically it was often difficult to time the murmur more accurately than to say that it followed closely the opening snap.

Relationship between the Opening Snap and the Degree of Mitral Valve Disease Present. Absence or softness of the opening snap was noted in four cases in the series. In three of these gross calcification of the mitral valve was present and this was diagnosed radiologically and on palpation at valvotomy ; in the fourth the stenosis was slight, as judged by the absence of symptoms and of generalized cardiac enlargement. One further case of gross calcification of the mitral valve was met, but in this the opening snap was not unusually soft.

These findings are in agreement with the observations of Rouchès (1888) that the opening snap was not heard when the stenosis was mild or in extreme cases where the valves had lost their suppleness and ability to snap. Wynn (1952) found an association between gross calcification of the mitral valve, softness of the first heart sound, and absence of the opening snap. Sellors (1952) suggests that the snapping quality of the first heart sound in mitral stenosis may be produced at the anterior cusp of the mitral valve and notes that if a finger is placed on this cusp during the operation

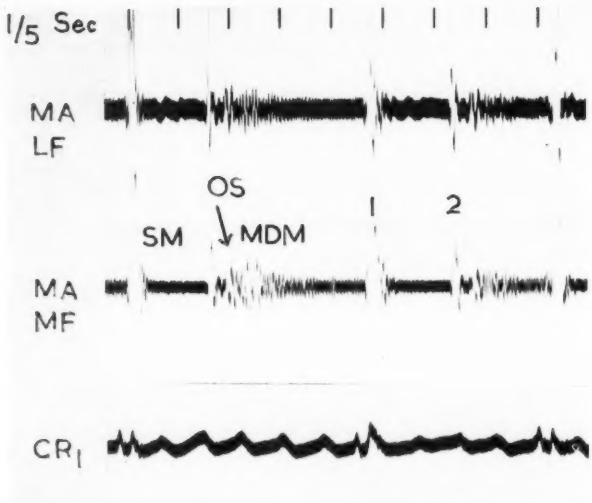

FIG. 4.—Time relationship between the opening snap (OS) and the mid-diastolic murmur (MDM). The murmur follows closely the opening snap. In the first complex there is an initial crescendo in the mid-diastolic murmur. MA=mitral area. MF and LF=medium- and low-frequency filters. 1 and 2=first and second heart sounds. SM=systolic murmur.

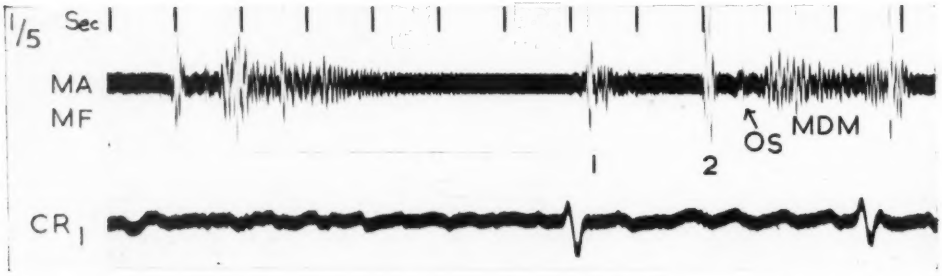

FIG. 5.—Time relationship between the opening snap and the mid-diastolic murmur. A short silent gap separates the opening snap (OS) from the beginning of the mid-diastolic murmur (MDM). MA=mitral area. MF=medium-frequency filter. 1 and 2=first and second heart sounds.

of valvotomy, as it balloons into the left atrium at the beginning of systole, the snapping quality of the sound, heard by listening directly to the heart with a stethoscope, is temporarily abolished. If, therefore, the diseased mitral valve itself gives rise both to the loud, abrupt, snapping first heart sound and to the opening snap, then the clinical association noted between the intensity of the two sounds in this series is explained.

DIFFERENTIATION OF THE OPENING SNAP FROM SPLITTING OF THE SECOND SOUND

Audible splitting of the second sound is physiological, provided auscultation is carried out in the pulmonary area ; the interval between the two components varies with respiration, tending to increase with inspiration (Potain, 1866 ; Leatham and Towers, 1951).

Splitting of the second sound in the pulmonary area was recognized clinically and confirmed on a high-frequency phonocardiogram in 31 cases in this series. Phonocardiography demonstrated its presence in a further case, in which clinically it could not be differentiated from the opening snap, on account of persistent tachycardia. In the majority (31 out of 33) both splitting of the second sound and an opening snap were present in the same patient (Fig. 6). It was not felt that the *quality* of the second component of a split second sound enabled it always to be distinguished from an opening snap.

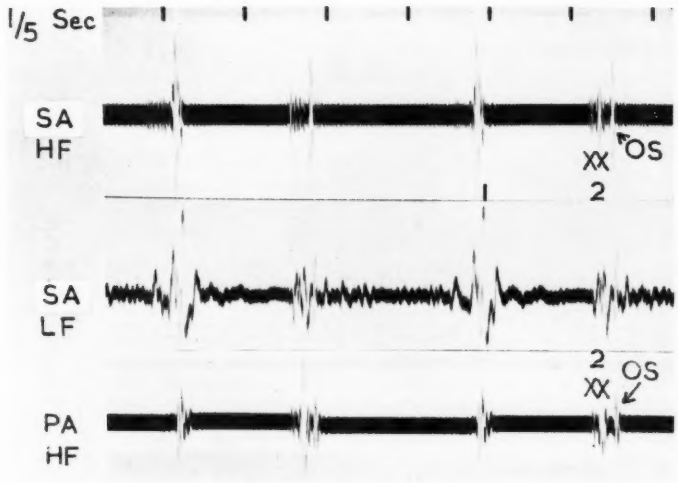

FIG. 6.—Splitting of the second sound (2xx) closely followed by the opening snap (OS). The second component of the split second sound is of greater intensity than the opening snap in the pulmonary area (PA). In the supra-mammary area (SA) the opening snap is the greater. HF and LF=high- and low-frequency filters.

The area where the second component of the second sound was best heard differed markedly from that of the opening snap. In every case the former was loudest in the pulmonary area and in only a minority was it equally well heard in other areas.

The *interval* between the beginning or first component and the second component of a split second sound varied between 0·01 sec. and 0·05 sec., and the average interval for the group was 0·03 sec. This average was in contrast to the average interval between the beginning of the second sound and the opening snap (0·07 sec.) (Fig. 2). It will be noted, however, that the maximum interval between the first and second components of the second sound and the minimum interval between the beginning of the second sound and the opening snap lay in the same range (0·03 to 0·05 sec.).

The effect of respiration on the width of splitting of the second sound was noted in most patients, the interval tending to lengthen on inspiration and to shorten on expiration. In six patients splitting of the second sound was only present on deep inspiration. Although phasic variation in amplitude of the opening snap was seen, the snap tending to be diminished in intensity during inspiration, no variation in its timing was noted during respiration.

DIFFERENTIATION OF THE OPENING SNAP FROM THE THIRD HEART SOUND

The criteria used for diagnosis of the third heart sound have been those put forward by Orias and Braun-Menendez (1939) and Rappaport and Sprague (1942). In quality it is predominantly

a low-frequency sound as opposed to the higher frequency of the opening snap. The mid-point of the third heart sound lies between 0·16 and 0·24 sec. after the beginning of the second sound. This is greater than the value of 0·03 to 0·14 sec. for the opening snap in this series. The third heart sound is usually best heard a little internal to the mitral area (Evans, 1942).

In no patient was a clear third heart sound recognized clinically, although a small third heart sound was present in the phonocardiogram in eight (Fig. 7). The rarity of the third heart sound in mitral stenosis is in contrast with the frequency of an opening snap.

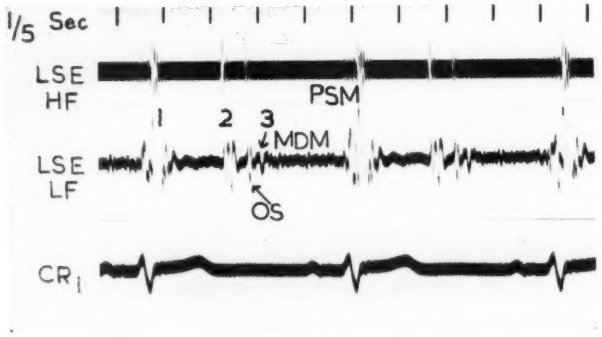

FIG. 7.—The third heart sound in the presence of an opening snap and a mid-diastolic murmur. A small third heart sound (3) is recorded during the beginning of the mid-diastolic murmur (MDM). It is preceded by the opening snap (OS). LSE=left sternal edge. HF and LF=high- and low-frequency filters. 1 and 2=first and second heart sounds. PSM=presystolic murmur. CR1=electrocardiogram in lead CR1.

Orias and Braun-Menendez (1939) suggested that the third heart sound was due to vibrations produced during rapid ventricular filling. In mitral stenosis left ventricular filling is slow, being impeded by the stenosis, and so there is diminution or absence of a third heart sound, which is replaced by the mid-diastolic murmur. When, on the other hand, incompetence is the only lesion in mitral valve disease, Brigden and Leatham (1952) have shown that an obvious third heart sound is a frequent finding : this is explained by rapid filling of the left ventricle through the widely patent mitral valve.

DISCUSSION

In this series clinical differentiation between an opening snap and the second component of a split second sound was generally possible, based on the site where the sound was best heard and on the interval that separated it from the first component of the second sound. The fact that in most cases both sounds were present was of great value in distinguishing each. Deep breathing was a manœuvre that sometimes aided clinical distinction between the sounds, since with this the splitting of the second sound tended to widen, or in some cases to appear *de novo*, while the intensity of the opening snap tended to diminish.

Cases with persistent tachycardia presented the greatest difficulty, for in these splitting of the second sound and an opening snap lay crowded into an interval of 0·03 sec. When carotid pressure induced a slower heart rate, differentiation of these three sounds was facilitated. In one patient, in whom this manœuvre failed, phonocardiography with a rapidly moving film showed the presence of both splitting of the second sound and an opening snap.

The differential diagnosis of the opening snap from a third heart sound seldom caused difficulty. Although a small third heart sound was recorded phonocardiographically in eight cases, clinically it was never audible.

The opening snap was found to be most useful for the diagnosis of mitral stenosis in patients in whom other signs were missing on casual examination. When the opening snap was heard by itself, it stimulated a more thorough search for a latent mid-diastolic murmur.

Although the pathogenesis of the opening snap remains in doubt, there is evidence that it is produced at the stenosed mitral valve itself. Margolies and Wolferth (1932) showed that the opening snap coincided with the beginning of the descent of the V wave in a jugular pulse tracing. Assuming that the tricuspid and mitral valves open almost simultaneously, the fall in jugular venous pressure following the opening snap strongly suggests that this sound is coincident with the opening of the mitral valve.

The association of the opening snap with mitral stenosis alone and its absence in other diseases causing pulmonary hypertension or pulmonary venous congestion is an argument in favour of its production at the stenosed mitral valve. Its tendency to become softer or disappear with extreme rigid calcified stenosis suggested that it is not directly related to any increase in left auricular pressure, which would remain unrelieved or tend to increase further with increasing stenosis, but rather to the state of the mitral valve itself. Its infrequency in early mitral valve disease when the diastolic murmur first appears (Thomas, 1952) suggests that considerable stenosis is required to produce it. Its absence in pure mitral incompetence (Guttman, 1872 ; Brigden and Leatham, 1952) emphasizes its essential connection with a stenotic lesion.

If it be assumed that the opening snap is produced at the mitral valve, then hæmodynamic factors may be used to explain its variable timing. The timing of the opening snap depends on the inter-relationship between the left atrial pressure and the rate of fall of left ventricular pressure during the phase of isometric relaxation. When the left ventricular pressure falls below the left atrial, the mitral valve opens with the production of the opening snap. Messer *et al.* (1951) have explained in the following way the finding that in patients in auricular fibrillation a short cardiac cycle is followed by an early opening snap. A short diastolic interval in mitral stenosis tends to cause an increase in left atrial pressure, due to inefficient emptying of the left atrium. In the subsequent diastole, therefore, left atrial pressure exceeds left ventricular pressure slightly earlier and hence the mitral valve opens earlier. The occurrence of an earlier opening snap, with increasing heart rate and hence shorter diastolic interval, in patients in sinus rhythm could be similarly explained. The diastolic interval, however, is only one of many factors affecting the left atrial pressure and left atrial pressure is not the only factor affecting the timing of the opening snap. Although, therefore, a relationship was seen in individual cases in our series between the diastolic interval and the timing of the opening snap, in the group as a whole no direct relationship was found.

Summary

A clinical and phonocardiographic study of 33 cases of mitral stenosis has been made. An opening snap was heard in 28: in a further 4 it was recorded on the phonocardiogram although not detected clinically; in these its soft character or the presence of tachycardia caused it to be missed clinically. In only one case was an opening snap absent in the phonocardiogram.

Differentiation of the opening snap from splitting of the second sound was made on the timing of the sounds and the area where they were best heard. The second component of a split second sound was always loudest in the pulmonary area and the opening snap usually loudest in the area above and internal to the left breast. The frequency with which both sounds were present (31 out of 33) made their recognition relatively easy. Phonocardiography was necessary to differentiate between them in only one case.

The physiological third heart sound differs from the opening snap in its low-pitched quality, the area where it is best heard and its timing. In no patient was a clear third heart sound recognized clinically, although in eight a small third heart sound was present in the phonocardiogram.

Absence or diminution in intensity of the opening snap was associated with gross calcification of the mitral valve in three cases and with slight stenosis in a fourth.

The opening snap was found to be a useful diagnostic sign, when other signs of mitral stenosis were missing on casual examination. Its presence should lead to a more thorough search, which should reveal the latent mid-diastolic murmur.

I would like to acknowledge with sincere thanks the help and criticism of Dr. William Evans in the preparation of this paper. I wish to thank Mr. W. D. Dicks for technical help with the phonocardiograms.

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CAVAL REFLUXES IN ANGIOCARDIOGRAPHY AND THE DYNAMICS OF THE RIGHT ATRIUM

BY

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During the past few years angiocardiography has become one of the routine methods in the investigation of congenital heart disease. The development of the technique has increased its diagnostic value so that it offers a method of judging not only the anatomical, but also the pathophysiological aspects of a heart disease. This paper deals with a problem often met with in angiocardiography, i.e. the regurgitation of dye from the right atrium into the venæ cavæ and their proximal branches, and its relation to the function of the right atrium. This phenomenon, which occurs especially in children, has sometimes been thought to have a special diagnostic value. Up to the present, however, no detailed investigation of the mechanism of this reflux appears to have been carried out.

Angiocardiographic Technique Used in the Present Investigation

The development of fast direct angiocardiography (10–12 exp./sec.) in two planes at an angle of 90°, with synchronous electrocardiographic recording, enables us not only to study the morphology but also to gain physiological and patho-physiological information, regarding the dynamics of the heart and may thus offer us a way of approaching the problem. The following is an account of some observations, using this method in cases with or without cardiac lesions interfering with the function of the right heart.

We have used the following amounts of contrast medium (umbradil, astra) in a 70 per cent solution, given intravenously.

Weight in kg.	*Dose, ml./kg. of weight*	
	Injection in cubital vein	Injection in malleolar vein
2·5—5	1·00—1·5	1·25—1·50
5—10	1·00—1·25	1·25
10—20	0·75—1·25	1·00—1·25

Within these limits, the amount given is governed by the cardiac volume. Satisfactory roentgenographic contrast, providing good or adequate visualization of all the heart cavities and the large vessels, can usually be obtained with these amounts of contrast medium. The speed of the injection has, as far as possible, been kept constant.

All children received a 2·5 per cent solution of avertin, 0·1 ml. per kilogram of weight by rectum and remained quiet, with shallow respiration, during the examination.

Anatomy and Physiology of the Venæ Cavæ

It seems reasonable that the orifices of the great systemic veins that terminate in the right atrium must close at the start of each atrial systole. Otherwise some of the force of the contraction would be spent in returning blood to the veins. Careful investigations have been carried out concerning the mechanism of closure of caval veins.

The *opening of the superior vena cava*, devoid of a valve, is situated at the upper and posterior part of the cavity. The orifice is elliptical in shape with a right anterior and left posterior margin (which are brought in contact with one another at the start of each atrial systole, thus closing the orifice). Among the muscle fibres peculiar to each atrium are annular fibres surrounding the extremities of the large vessels, as they

open into the atrium. Keith (1902) has especially studied the structures that close the venous orifices of the right atrium and according to him four muscular bands bring this about (tænia terminalis, superior and inferior limbic bands, and the septal band). Further, the terminal half inch of the superior vena cava is surrounded by loops of muscle fibres which are regarded as the only representative of the musculature of the sinus venosus now remaining in the mammalian heart.

The *orifice of the inferior vena cava* is situated at the lower and posterior part of the atrium and bounded anteriorly by the vestigal valve of the inferior vena cava. In addition, there are annular muscle fibres present which surround the opening.

According to experimental evidence the venous orifices remain patent during atrial systole and the physical forces that prevent regurgitation are the following (Wiggers, 1949): (*a*) the necessity of stopping the onflowing blood before the stream can be reversed, (*b*) the fact that pressure is lower in the ventricles than in the veins so that the atria tend to empty in the direction of least resistance, (*c*) the peristaltic mode of contraction which favours emptying towards the ventricles, and (*d*) the emptying of the atria during early ventricular diastole so that they contain but a small quantity of blood when the atria contract.

Angiocardiographic Observations

Dynamics of the right atrium. The right atrium contracts mainly in the antero-posterior direction, the reduction in height being less marked. This agrees with the anatomical finding that the lateral fornices of the caval veins are connected by the sulcus terminalis, an " indifferently marked fibrous septum " (Keith, 1902). The distance between the lateral fornices of the caval orifices is, therefore, scarcely altered in contraction of the atrium. A peristaltic mode of contraction has not been observed. The contraction starts at the summit of the P wave and the atrium is small at the Q wave in the synchronous electrocardiogram. It seems to become slightly smaller during the Q–S interval—perhaps due to the closure of the tricuspid valve. The refilling of the atrium begins about a hundredth of a second after the S wave. It is rapid to start with, but slow from the end of the T wave to the P wave. Sometimes we have noticed some reduction in its size just after the end of the T wave due to the passage of blood into the right ventricle, the A-V valve opening at this point. In infants with a rapid heart rate (120–180 a minute) the A-V valve seems, however, to remain closed till the atrium contracts, indicating that the pressure in the right atrium only then becomes greater than in the right ventricle. The filling of the ventricle in these cases thus occurs during the short interval from the point of the P wave to the Q wave.

The dynamic importance of atrial contraction has been much debated. It has been demonstrated that filling of the ventricle occurs mainly during early diastole, due to the difference in atrial and ventricular pressure at the end of the isometric relaxation. In infants, with their rapid heart rates the atrial contraction seems, however, to be the chief force that fills the ventricle.

The relation of the size of the right atrium in maximum atrial systole and diastole, as seen in angiocardiograms, is approximately 1 : 3 or 1 : 4 (Fig. 1).

Refluxes of Contrast during Injection via the Superior Vena Cava

If the dye reaches the orifice of the superior vena cava during atrial systole it is stopped. The calibre of the vein, except in the proximal part, increases and sometimes there is retrograde filling of its small tributaries. The most proximal part of the vein, however, shows a circular narrowing during atrial systole. It appears in most cases even during the injection of contrast medium and seems, therefore, to be an indication that this portion of the vein takes an active part in the atrial contraction (Fig. 1).

When the atrium has become contrast-filled through the superior vena cava we sometimes see, even in normal cases, dye leaving the atrium through the inferior vena cava. This happens only during atrial diastole when the orifices of the caval veins are not closed.

In the pathological conditions that interfere with the function of the right side of the heart, for instance atrial or ventricular septal defect, refluxes are regularly seen down into the inferior vena cava. They are seen also during atrial systole, from the peak of the P wave to just after the S wave but they occur most often and have their maximum intensity in the latter half of the interval (Fig. 2).

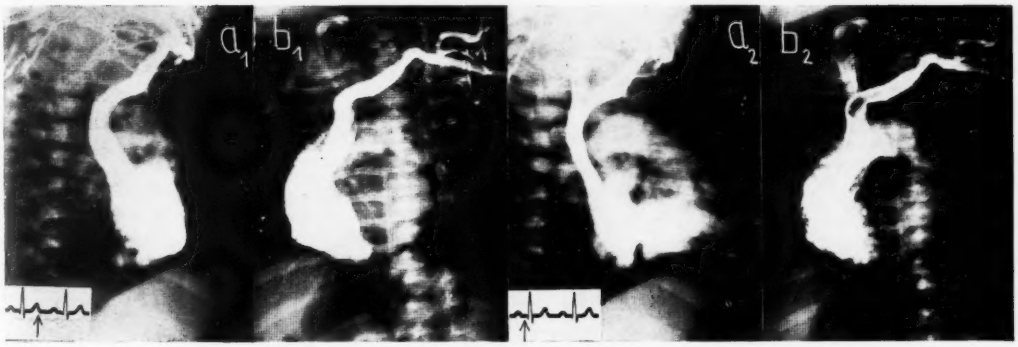

FIG. 1.—Narrowing of the superior vena cava simultaneously with atrial systole.

Figures a_1, a_2 in the right anterior oblique and b_1, b_2 in the left anterior oblique position.

a_1b_1: The atrium is seen to be biconvex. The superior vena cava is broad.

a_2b_2: During atrial systole the superior vena cava contracts, as demonstrated by a marked diminution in the calibre of the proximal part of the vessel.

FIG. 2.—The closure of the orifice of the superior vena cava and demonstration of systolic reflux downwards into the inferior vena cava in a case of atrial septal defect with left to right shunt.

Injection of contrast medium is done through an antecubital vein.
Left anterior oblique position.

b_1: The dye on its way through the left innominate vein. Beginning of atrial systole with a retrograde filling of the small venous tributaries.

b_2: End of the same atrial systole. The dye has reached the closed orifice of the superior vena cava. Large refluxes of dye up into the internal jugular veins.

b_3: One-tenth of a second later. The right atrium becomes opacified instantly with the contrast medium which has accumulated in the afferent veins.

b_4: In the following atrial systole there is a large reflux of diluted dye downwards into the hepatic veins. The dilution of dye in the right atrium may be due to a left to right atrial shunt.

Refluxes of Contrast during Injection via the Inferior Vena Cava

Here the contrast medium reaches the right atrium from below and if it arrives at the orifice during atrial systole it is held up and directed downwards into the hepatic veins (Fig. 3).

In contrast with the superior vena cava the proximal part becomes dilated in atrial systole and thin in diastole when the passage into the atrium is free.

When the atrium is heavily contrast filled, i.e. dye has filled the atrium during the whole of diastole, dye sometimes passes upwards into the superior vena cava during the end of diastole,

even in normal cases (Fig. 4). In atrial or ventricular septal defects, with left-to-right shunts, systolic refluxes downwards into the inferior vena cava are a regular finding. Refluxes up into the superior vena cava are less common. In relation to the electrocardiogram they occur during the interval from the top of P to just after the S wave, the maximum regurgitation taking place at the end of the P–S interval.

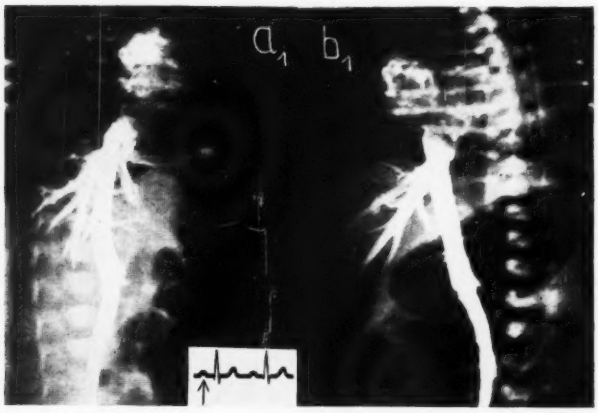

FIG. 3.—Closure of the inferior vena cava and demonstration of a systolic " pseudo-reflux " into the hepatic veins.
Injection of dye into a malleolar vein.
The dye has reached the orifice of the inferior vena cava during atrial systole. No dye enters the atrium. The vena cava is wide and some dye is diverted downwards into the hepatic veins.
b_1: In b_1 it can be seen that the dye is about equally distributed between the right and left atria, due to an atrial septal defect.
a_1: In a_1 it is seen that only an insignificant amount of dye has so far passed into the ventricles.

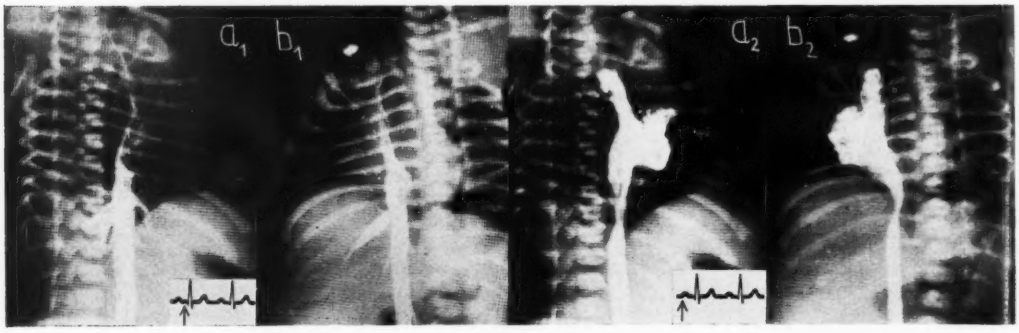

FIG. 4.—Closure of the inferior vena cava and demonstration of a reflux during atrial diastole.
Injection of dye into a malleolar vein.
a_1, a_2 in right anterior oblique, b_1, b_2 in left anterior oblique position.
a_1b_1: The inferior vena cava is broad in atrial systole. Its orifice is closed, permitting only a fine stream of dye to enter the atrium.
a_2b_2: Right atrium is densely opacified. The large auricular appendage is seen. Dye passes out in a broad stream through the open orifice of the superior vena cava.
Note that the superior vena cava is broad and the inferior vena cava thin in atrial diastole.

Discussion

The refluxes seen during angiocardiography are of essentially different origins.

Pseudo-refluxes. Here the contrast medium never has been in the atrium. Due to the closure of the caval orifice during atrial systole the dye is held up and there occurs a retrograde filling of the venous tributaries. These refluxes are seen in normal hearts as well as in all sorts of congenital cardiac lesions.

True Refluxes. Here the dye leaves the right atrium through one of the venæ cavæ. They occur most often downwards into the inferior vena cava, which is in agreement with clinical experience and anatomical investigations that have shown that this orifice is the weakest point of the right atrium.

Refluxes occurring in Atrial Diastole. These are often seen in congenital malformations of the heart with increased right atrial pressure and sometimes even in normal hearts. The mechanism seems to be an overloading of the atrium with contrast medium from the injection. Consequently, at the end of atrial diastole before contraction has started, the atrial pressure becomes higher than in the vena cava not used for injection and some dye passes out through its open orifice.

Cardiac catheterization studies in adults have indicated that rapid injections of dye do not significantly alter the right atrial pressure. In view of the short distance between the site of injection and the right atrium in small children and infants, an elevation of the atrial pressure may, however, be possible. In children the amount of contrast medium used is relatively greater than in adults. In atrial diastole the open caval orifices seem, however, to serve as safety valves and thus the increase in atrial pressure during angiocardiography may be small, if perceptible.

There appears to be little doubt that these refluxes, as well as the pseudo-refluxes, are produced by the injection of dye. They are consequently more frequent the younger the infant and the greater the amount of dye injected per second. They disappear rapidly and occur only during and immediately after the injection. It is obvious that the synchronously recorded electrocardiogram is of great importance for the identification of these refluxes as well as the pseudo-refluxes.

Refluxes occurring in Atrial Systole. In most cases true refluxes, however, occur during and most commonly at the end of atrial contraction. This may be explained by the fact that the start of effective mechanical contraction corresponds to the summit of the P wave in the simultaneous electrocardiogram, but the maximum pressure is not reached until about 0·02 sec. later. Further, it is seen that the right ventricle becomes rapidly filled in early diastole to a point beyond which further distension may be resisted. That refluxes are noted corresponding to the Q–S intervals may be due to the fact that shortly after the onset of ventricular contraction the atrial pressure rises abruptly, following closure of the A-V valve, which bulges into the atrium. It is probable that the course of the atrial pressure curve depends upon the heart rate and the contribution by atrial systole to ventricular filling.

By using optical manometers to record pressure changes in the atria and ventricles it has been found that the maximum atrial pressure coincides with the isometric contraction of the ventricles (Wiggers, 1948). By catheterization of the heart the atrial pressure is found to be lower at the beginning of the isometric contraction of the ventricle than at the start of the atrial systole, and that the isometric ventricular contraction produces only a little quick and sharp rise in the pressure (Lagerlöf and Werkö, 1948). The presence of the catheter, introduced through one of the caval orifices may, however, modify the normal pressure curve. None of the methods seem, therefore, able to give exact information about the atrial pressure variations.

Refluxes of dye during atrial systole are not seen in normal cases. In this phase of the heart cycle the caval orifices are closed and no dye is entering or leaving the heart. The increase in diastolic filling due to the injection is not followed by an increase in the systolic atrial pressure sufficient to break the closure mechanism of the caval orifices.

In congenital heart lesions where there is an extra load on the right atrium, as in atrial or ventricular septal defects with significant left-to-right shunts, tetralogy of Fallot, etc., systolic

refluxes are on the other hand regularly seen—even when a small amount of dye is used (Fig. 5 and 6). In angiocardiograms from such cases the refluxes are seen to occur not only in the contrast-loaded heart cycles during the injection but for quite a long time afterwards. They have a diagnostic value, representing a visualization of a patho-physiologic phenomenon.

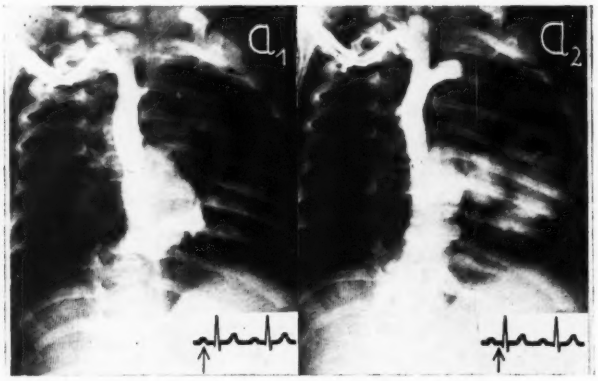

FIG. 5.—Incompetence of the inferior caval orifice in a case of tricuspid atresia.
Injection of dye through the right antecubital vein.
Right anterior oblique position.
a_1: Atrial diastole. The superior vena cava and right atrium are filled with contrast medium.
a_2: During atrial systole there is a heavy reflux downwards into the dilated inferior vena cava and hepatic veins.

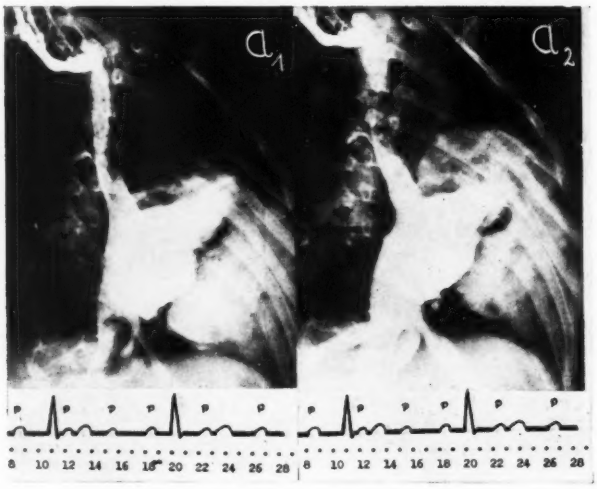

FIG. 6.—Simultaneous atrial and ventricular systole in a case of complete heart block.
Injection of contrast medium is done through the right antecubital vein.
Right anterior oblique position.
a_1: Right atrium in diastole, right ventricle in systole (exposure nr. 11 in the accompanying electrocardiogram).
a_2: Atrial systole occurs before the ventricular contraction is finished. Heavy reflux occurs downwards into the inferior vena cava, but there is also a retrograde filling of the superior vena cava. Sinus venosus is also seen opacified in the atrio-ventricular groove (exposure nr. 13 in the accompanying electrocardiogram).

The explanation for their existence in these cases is complex. There is often a dilation of the right atrium perhaps combined with a weakening of the closure-mechanism of the caval orifices. Further, there is an increased atrial pressure, which may become even higher following the injection and reach the critical level of resistance of the orifices. Nearly always, however, the entrance of the dye is stopped during atrial systole.

Other factors possibly involved in the origin of refluxes must be considered. No specific effect of the contrast medium on the myocardium can be expected during the observation period which lasted only up to 1 second after dye has reached the heart. Such effects are met with 1–2 seconds later. Neither does respiration seem to have any influence on the reflux mechanism in our study. All children were well anæsthetized. They were completely quiet during angiocardiography (with shallow regular respiration). The interval between the films, i.e. the observations, are also very short. Therefore changes in the intrathoracic pressure must be small and may be considered negligible.

Summary

Refluxes of contrast medium from the right atrium into the venæ cavæ and their relation to the dynamics of the right atrium have been studied by fast angiocardiography (10–12 pictures a second in two projections at right angles) with simultaneous electrocardiographic registration. It has been shown that the caval orifices are normally closed during atrial systole. The refluxes have been classified according to their origin. Their significance is discussed with emphasis on the importance of simultaneous electrocardiographic registration for diagnostic differentiation.

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ANOMALOUS RIGHT SUBCLAVIAN ARTERY

BY

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Abnormalities in the course of the arteries arising from the aortic arch are not uncommon. These vessels may arise from as many as five or from as few as two main trunks and their order of origin may also vary. An aberrant right subclavian artery arising as the last vessel from the aortic arch is a relatively frequent form of these congenital anomalies.

Of the early descriptions of this condition, Bayford's in 1794, is perhaps the best known, although Hunauld has been credited with the first report in 1735. Holzapfel (1899) found reports of 193 human specimens showing the anomaly and added 5 of his own: he gave an incidence of 0·6 per cent in the post-mortem material examined in this series. Cairney (1925) described two anatomical specimens and found reports of an additional 19 in a total of 2494 necropsies, an incidence of 0·8 per cent.

In 1936 the anomaly was first recognized during life by Kommerell during the course of a barium meal examination. Other single cases were diagnosed radiologically by Zdansky (1939), Gunsel (1940), Copleman (1945), and Stauffer and Pote (1946). Two examples were described by Dahm (1940) and two by Ravelli (1950). Anatomical confirmation was obtained in Zdansky's patient only, who was examined post mortem.

During the last five years an increasing number of cases have been recorded. Brean and Neuhauser described 15 examples in 1947. Felson *et al.* (1950) describe their findings in nine patients without symptoms, in all of whom the radiological diagnosis was made by study of the barium filled œsophagus. Apley (1949) by angiocardiography in a child demonstrated the course of the vessel between the œsophagus and trachea. Kreutzer *et al.* (1950) showed it in the same position in a child with Fallot's tetralogy: their observations were confirmed at necropsy. Raphael *et al.* (1952) passed a radio-opaque catheter from the right brachial artery through the right subclavian artery into the aorta to confirm that the impression on the posterior wall of the œsophagus was due to the anomalous course of the right subclavian artery.

Bahnson and Blalock (1950) encountered 18 instances of aberrant right subclavian artery and 18 cases of aberrant left subclavian artery in 841 patients operated on for suspected congenital pulmonary stenosis. Gross and Neuhauser (1951) found 10 examples in a series of 40 babies operated on for the relief of tracheal or œsophageal obstruction.

Anatomy and Embryology

The anomalous right subclavian artery may arise from the medial or upper aspect of a normal left-sided aortic arch or less commonly at the junction of the arch and descending aorta. Its origin is on the left of the mid line and caudal to the origin of the left subclavian artery. Typically the vessel courses upwards and to the right, posterior to the œsophagus and emerges from the thorax over the first right rib (Fig. 1).

Frequently the artery is dilated at its origin or arises from an aortic diverticulum. Holzapfel described this in 33 out of 55 cases in which the size of the vessel was recorded. He also found that although the artery was usually retro-œsophageal, it passed between the œsophagus and trachea in 15 per cent and anterior to the trachea in 5 per cent of his series.

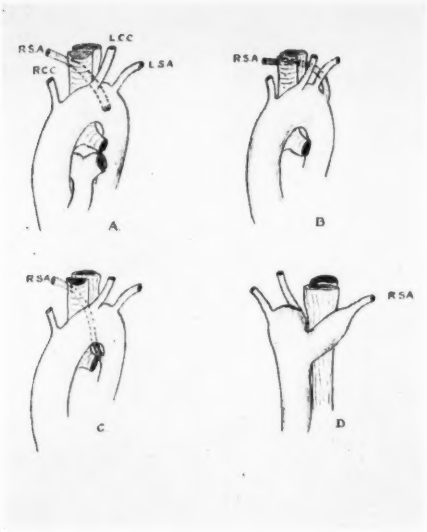

FIG. 1.—The anterior views (A), (B), and (C) show variations in the origin of the anomalous right subclavian artery. The posterior view (D) demonstrates the vessel that is dilated at its origin.

There is also a very rare type of anomalous right subclavian artery, the only known example being a post-mortem specimen described by Edwards in 1948. The aorta ascended normally to the left of the œsophagus and then turned posterior to it to reach the right side of the mid line. The descending aorta lay to the right of the spine and at its junction with the arch an aortic diverticulum was present. The right subclavian artery originated from this diverticulum as the fourth branch of the arch and passed upwards and to the right to reach the first rib.

Embryology. The transformation of the embryonic aortic arch system has been described in the classical work of Congdon (1922). Cairney (1925) has dealt with the developmental aspects of the anomalous right subclavian artery in detail. The generally accepted view is that the caudal segment of the right dorsal aorta fails to become absorbed and is incorporated in the origin of the right subclavian artery. It may remain dilated and so form an aortic diverticulum. The right fourth aortic arch and cephalic portion of the right dorsal aorta which normally give origin to the right subclavian artery cease to function and disappear completely. As a result the right subclavian artery arises from the aortic arch distal to the origin of the left subclavian artery and in the majority of instances runs a retro-œsophageal course. The first vessel arising from the aortic arch is usually the right common carotid artery, followed by the left common carotid and left subclavian arteries, the right subclavian artery being the last branch of the aortic arch. Holzapfel gives nine other variations in the origin of these vessels.

It is difficult to explain how the aberrant right subclavian may come to lie anterior to the trachea or between it and the œsophagus. Holzapfel has suggested that of the many vascular roots which are available in the embryo, an unusual one is preserved. Thus in the very early stage of development some anastomotic channel lying anterior to the foregut may have reached a high state of development.

RADIOLOGICAL FINDINGS

The diagnosis can be made on the characteristic appearances of the barium filled œsophagus as described by Neuhauser (1946) and by others. In the postero-anterior view the artery produces an oblique indentation on the posterior œsophageal wall (Fig. 2 and 3). This starts on the left side

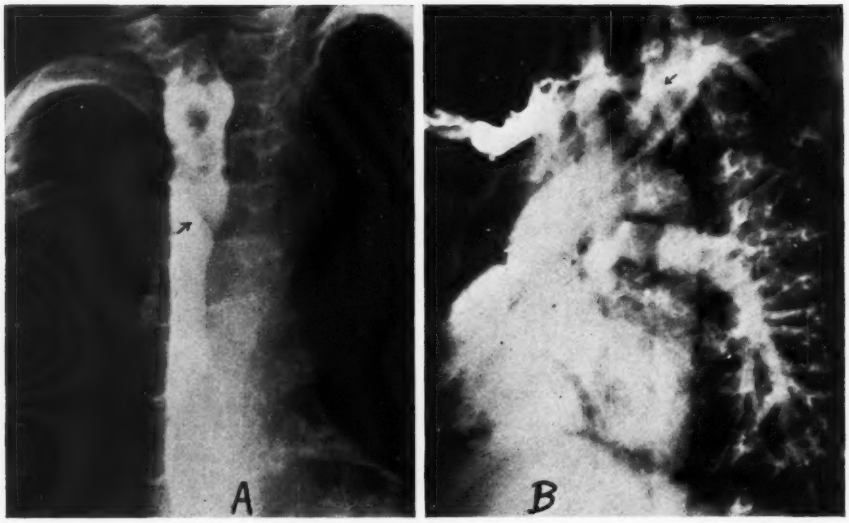

FIG. 2.—A.P. position. Case 1, aged 4 years. Fallot's tetralogy. (A) A faint oblique impression can be seen on the posterior œsophageal wall passing upwards and to the right from the level of the aortic arch. (B) Angiocardiogram at 2 sec. in the L.A.O. position. The right subclavian artery arises posterior to the left subclavian artery and passes upwards, forwards and to the right.

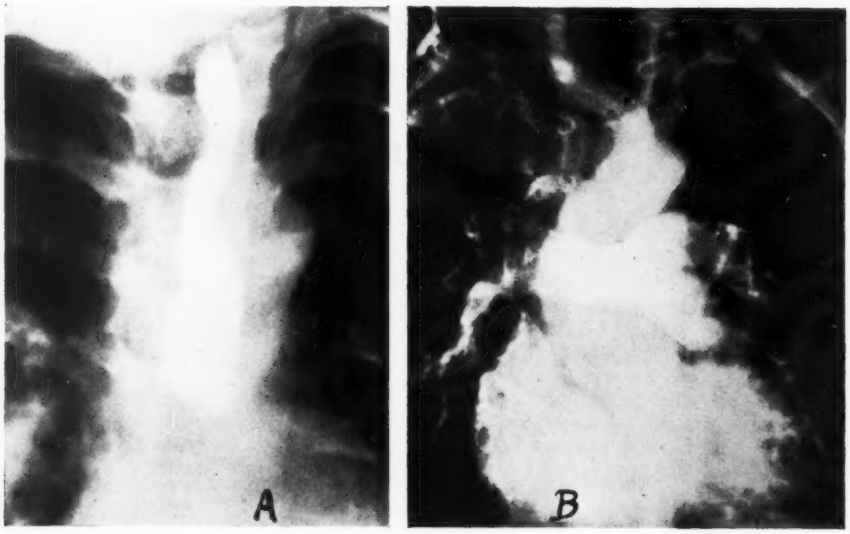

FIG. 3.—A.P. position. Case 2, aged 4 years. Fallot's tetralogy. (A) Broad oblique indentation present on the œsophagus running up and to the right from the level of the aortic arch. (B) Angiocardiogram at 2¼ sec. in A.P. position. The proximal part of the right subclavian artery is visible on the left side of the right common carotid artery.

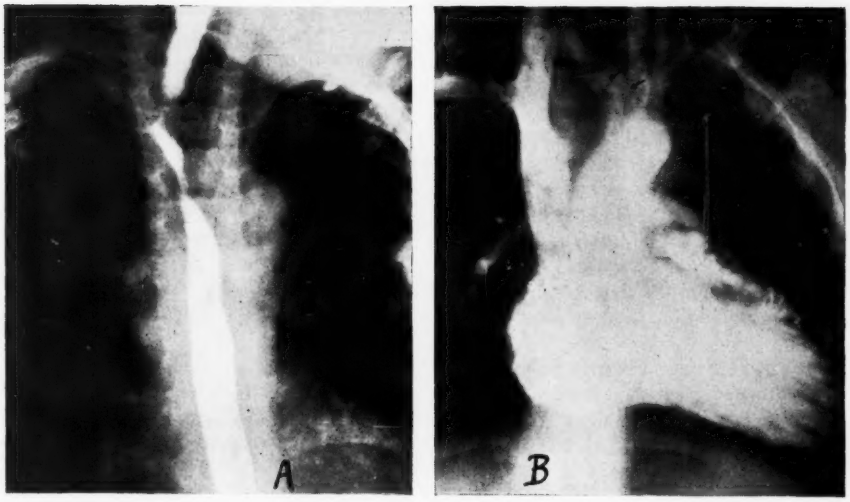

FIG. 4.—A.P. position. Case 3, aged 3½ years. Fallot's tetralogy. (A) Film shows an oblique impression on the posterior wall of the œsophagus a little above the level of the aortic arch. The œsophagus is slightly displaced to the right. (B) Angiocardiogram at 2 sec. in A.P. position. The proximal part of the right subclavian artery can be seen on the left side of the right common carotid artery.

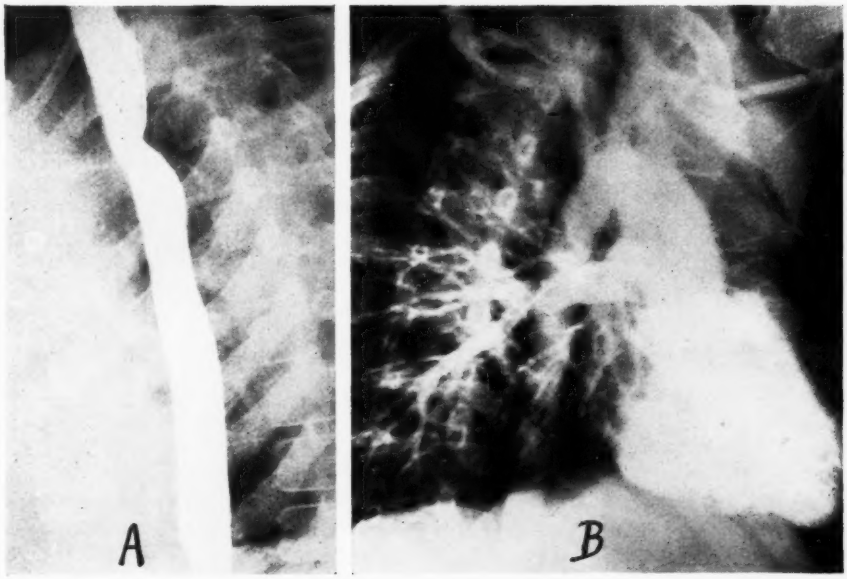

FIG. 5.—L.A.O. position. Case 4, aged 7 years. Fallot's tetralogy. (A) An angular impression is shown on the posterior wall of the œsophagus in the oblique position. (B) Angiocardiogram at 2 sec. in R.A.O. position. The right subclavian artery arises at the junction of the arch and descending aorta, runs upwards and to the right to the first rib.

of the œsophagus just above the aortic arch impression and passes upwards and to the right. Commonly the defect is about 5 mm. wide, but may be 15 mm. or more if the artery is dilated at its root or it arises from an aortic diverticulum. The indentation may be deepest towards the left side of the œsophagus and fade out on the right side or there may be an impression on the right side of the œsophagus as well (Fig. 3 and 4). When a large bolus of barium is swallowed the indentation may be completely obscured in this position.

The course of this artery is best seen in the lateral view (Fig. 6B). There is a semicircular impression on the posterior œsophageal wall at about the level of the aortic arch with narrowing of the œsophageal lumen. If the artery runs fairly obliquely the impression will be more angular. The size of the defect will of course vary with the size of the retro-œsophageal artery. The impression is usually well seen in the L.A.O. position (Fig. 5A) and its oblique course can be appreciated. In the R.A.O. position the defect may be less obvious although in some cases it is clearly shown. Transmitted pulsation on the posterior œsophageal wall at the level of the artery can be detected in some cases.

These typical appearances may be modified. If the aortic arch is unusually high the artery will produce an almost horizontal impression. If it arises from a low arch it will pass almost vertically upwards. When the root of the subclavian artery is dilated, its impression on the œsophagus is not only large but there is also forward displacement of the œsophagus as in the cases described by Dahm, Kommerell, Ravelli, and others. Should the artery pass between the œsophagus and trachea it will produce an oblique indentation on the anterior œsophageal wall as illustrated by Neuhauser (1946). No case of the vessel passing anterior to the trachea appears to have been diagnosed in life.

Differential Diagnosis. Narrowing of the lumen and displacement of the œsophagus may be produced by tumours in the wall or lumen of the œsophagus, mediastinal tumours, or enlarged mediastinal glands. These abnormalities can be excluded without much difficulty by careful fluoroscopy and adequate radiographs.

Vessels other than the subclavian artery may pass behind the œsophagus. A right-sided aorta with retroœsophageal arch and left descending aorta can be recognized by the presence of the aortic knuckle on the right. When the aortic arch and descending aorta are both on the right there may also be a retro-œsophageal left subclavian artery, innominate artery, or ductus arteriosus. The indentation due to the left subclavian and innominate arteries will pass obliquely upwards and to the left. The defect produced by the ductus arteriosus lies below the level of the aortic arch. In pulmonary atresia large collateral vessels passing from the aorta to the lungs are a not uncommon cause of indentations on the œsophagus: these impressions will be seen usually below the level of the aortic arch.

The aberrant right subclavian artery produces fairly characteristic changes on the barium-filled œsophagus. The diagnosis can be confirmed by angiocardiography when the abnormality can be detected in the P.A. view, and is well shown in the L.A.O. view. Confirmation can also be obtained if necessary by passing a catheter up the right radial artery into the aorta as described by Raphael *et al.* (1952).

Symptoms

The condition is usually asymptomatic and is diagnosed incidentally at fluoroscopic examination of the heart or gastro-intestinal tract.

Occasionally the artery indents the œsophagus sufficiently to cause dysphagia. This is commonest in infancy, and may be severe enough to warrant surgical division of the vessel. In many cases dysphagia consists of only mild hesitation in swallowing or regurgitation of feeds if these are not taken slowly. There may be delay in swallowing solids but not fluids or the reverse can occur. As the infant grows older there is a strong tendency for the spontaneous relief of symptoms.

Dysphagia may appear or recur in adults. Bayford described how a woman experienced dysphagia of gradually increasing intensity since childhood. She died at the age of 62 from

inanition and at necropsy the artery was found passing between the œsophagus and trachea. Bayford gave the name *Dysphagia Lusoria* to difficulty in swallowing produced by an aberrant right subclavian artery.

Symptoms other than dysphagia are uncommon. In the case described by Kellock and Batten (1895) death occurred following lodgement of food in the upper œsophagus. The child was cyanosed and dyspnœic: breathing ceased and death ensued in spite of tracheotomy. Post mortem, in addition to the anomalous right subclavian artery, the two carotid arteries were found to arise practically together. The right common carotid artery crossed in front of the trachea to reach the right side, and it seems that the respiratory difficulty resulted from the trachea being pushed forwards against it. Kreutzer *et al.* (1950) believed that pressure on the back of the trachea by the anomalous vessel, which passed anterior to the œsophagus, probably contributed to the dyspnœa present in their case of Fallot's tetralogy.

One case of fatal hæmorrhage due to perforation of the retro-œsophageal vessel by a fish bone was recorded by Kirby in 1818.

Case Reports

Case 1. A boy, aged 4 years. Cyanosis and dyspnœa had been present since early infancy. A clinical diagnosis of Fallot's tetralogy was supported by angiocardiography and at operation. At routine fluoroscopy in the P.A. position, an indentation was detected on the œsophagus commencing at the summit of the aortic arch and passing upwards and to the right (Fig. 2A). The lateral and L.A.O. positions showed that the impression was retro-œsophageal. Angiocardiography demonstrated pulmonary infundibular stenosis and over riding aorta. In the L.A.O. view a film at two seconds showed clearly the course of the right subclavian artery (Fig. 2B).

An end-to-side subclavian-pulmonary anastomosis was performed by Mr. T. Holmes Sellors. No attempt was made to dissect out the right subclavian artery which was not required for the anastomosis.

Case 2. A girl, aged 4 years. Cyanosis was noted first when the infant began to crawl and there was a history of dyspnœa on exertion. Fallot's tetralogy was diagnosed.

On screening a faint oblique impression on the posterior œsophageal wall was noted lying just above the aortic arch in the P.A., lateral and oblique positions. It was broader than that in Case 1 (Fig. 3A). It was most obvious in the lateral and L.A.O. views. The angiocardiogram in the A.P. position demonstrated pulmonary infundibular and valvular stenosis. A film at 2¼ sec. showed absence of the innominate artery. The proximal part of the right subclavian artery was seen clearly on the left side of and partly overlapping the right common carotid artery (Fig. 3B).

End-to-side anastomosis between the left subclavian and left pulmonary arteries was performed by Mr. Holmes Sellors. There was no necessity to dissect out the right subclavian artery.

Case 3. A girl, aged 3 years. Another case of Fallot's tetralogy with cyanosis present since birth and dyspnœa on exertion.

At fluoroscopy an oblique indentation was visible on the posterior wall of the œsophagus lying a little above the aortic arch. At this level the œsophagus was very slightly displaced to the right (Fig. 4A). Angiocardiography in the A.P. position demonstrated a pulmonary infundibular stenosis and over-riding aorta. The film at two seconds showed an identical appearance to that in Case 2; absence of the right innominate artery and the proximal part of the right subclavian artery lying to the left of the right common carotid artery (Fig. 4B).

Case 4. A boy, aged 7 years. There was a history of moderate cyanosis at rest and severe cyanosis with dyspnœa on exertion. A diagnosis of Fallot's tetralogy was made.

At fluoroscopy in the P.A. position the œsophagus appeared normal but in the L.A.O. and lateral views an oblique indentation was seen on the posterior wall of the œsophagus. The œsophagus was displaced slightly forwards at this level (Fig. 5A). Angiocardiograms in the A.P. position showed a pulmonary stenosis and over-riding aorta. The first part of the right subclavian artery lay on the left side of the right common carotid artery. The appearances were similar to those shown in Fig. 3B and 4B. On the angiocardiogram film taken at two seconds in the R.A.O. position the right subclavian artery can be seen to arise at the junction of the arch and the descending aorta. From this point the vessel ascends before turning laterally over the first rib (Fig. 5B).

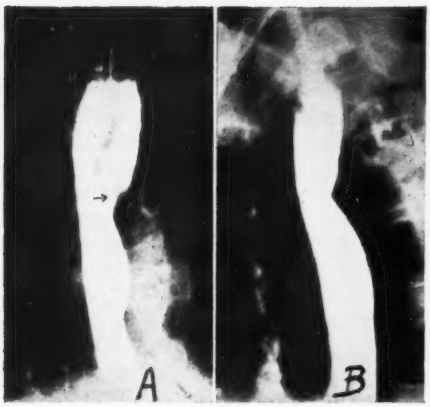

FIG. 6. Case 5, aged 46 years. (A) Antero-posterior position. (B) Lateral position. There is an indentation on the left wall of the œsophagus ½ inch above the aortic arch. From it a faint defect passes upwards and to the right. The indentation is shown clearly in the lateral view.

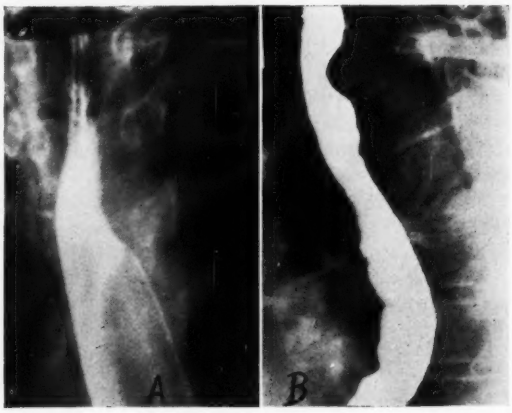

FIG. 7.—Case 7, aged 60. (A) A.P. position. The aberrant artery does not produce a visible defect on this film. (B) Extreme L.A.O. position with patient supine, showing gastro-œsophageal reflux and a large semicircular defect on the posterior wall of the œsophagus at the level of the aortic arch.

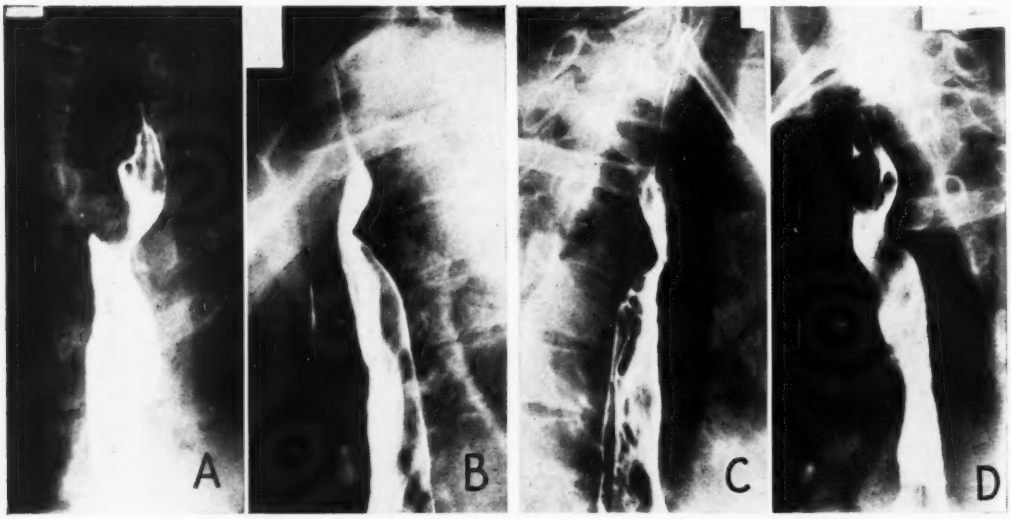

FIG. 8.—Case 6, aged 55 years. (A) There is a broad oblique impression running upwards and to the right from just below the summit of the aortic arch. It is most prominent on the right side of the œsophagus. (B) Lateral position. The œsophagus is slightly displaced forwards and there is a deep indentation on its posterior wall. (C) R.A.O. position and (D) L.A.O. position. The oblique impression is well shown in these views.

Case 5. A woman, aged 46 years. The patient complained of attacks of nausea and epigastric discomfort on and off for the past 14 years. A barium meal examination demonstrated a duodenal ulcer. A semicircular indentation on the left side of the œsophagus ½ inch above the summit of the aortic arch was also noted. A defect ran upwards and to the right of this indentation and gradually faded out towards the right side of the œsophagus. In the L.A.O. and lateral positions an indentation was visible on the posterior œsophageal wall (Fig. 6).

Case 6. A woman, aged 55 years. This patient was suffering from scleroderma, Reynaud's phenomenon, and rheumatoid arthritis. There was no history of dysphagia and no changes of scleroderma were detected in the gastro-intestinal tract at a barium-meal examination. However, a broad oblique impression was seen on the posterior œsophageal wall commencing just below the top of the aortic arch, and also a small indentation on the right side of the œsophagus (Fig. 8). These impressions were unlike those due to a double aortic arch (with small posterior arch) and there was no indentation on the trachea in P.A. or lateral views.

Case 7. A woman, aged 60. There was a 20-year history of epigastric pain and more recently heartburn one hour after food. There was no dysphagia or vomiting. During a barium-meal examination free gastro-œsophageal reflux occurred when the patient lay on her right side, while in the Trendelenberg position. No hiatus hernia could be demonstrated. Lateral and oblique views showed a wide semicircular indentation on the posterior œsophageal wall at the level of the summit of the aortic arch. The impression of the artery was very difficult to see in the P.A. view, being easily obscured by the barium bolus (Fig. 7).

Discussion

In the seven cases of aberrant right subclavian artery encountered during a period of 14 months, there was no history of dysphagia or other symptoms referable to the anomalous vessel. Fallot's tetralogy was diagnosed in four of them. During this time 5407 fluoroscopic examinations were carried out involving visualization of the œsophagus by barium and 90 of these were in patients with clinical evidence of congenital heart disease. Hence the evidence of aberrant right subclavian artery in this radiological department is 0·13 per cent and amongst patients with congenital heart disease investigated at this hospital the incidence is 4·4 per cent. These figures do not reflect the true incidence of the anomalous vessel in congenital heart disease in general since they are influenced by the selected nature of congenital lesions coming for examination to a cardiac surgical centre. During the period under review, fluoroscopy was carried out in 44 cases of Fallot's tetralogy and in 33 the aortic arch lay on the left side. Thus the incidence of the 4 cases of aberrant right subclavian artery in this condition is 12 per cent. The overall incidence in this series is much less than the incidence of 0·6 per cent found by Holzapfel (1899) in post-mortem material. In adults the anomalous vessel may cause little or no œsophageal deformity in the P.A. and R.A.O. positions and possibly a number of cases have not been detected at routine fluoroscopy. In children with congenital heart disease the barium filled œsophagus is scrutinized with great care, especially in the region of the aortic arch, and even minor indentations are less likely to be overlooked.

Brean and Neuhauser (1947) were the first to draw attention to the combination of this anomalous vessel and congenital heart disease. The incidence of 12 per cent in Fallot's tetralogy found in our series suggests that the aberrant artery is more commonly associated with this condition than with a normal heart.

The recognition of a retro-œsophageal vessel may be of more than academic interest. Dysphagia and stridor are well-known symptoms of double aortic arch and may even cause death in infancy or childhood. Severe dysphagia is much less common with an aberrant right subclavian artery but in these cases complete relief of symptoms can be obtained by surgical division of the first part of the artery as described by Gross and Ware (1946). The arm receives an adequate blood supply through collateral vessels communicating with the second and third parts of the subclavian artery.

The presence of a retro-œsophageal vessel can be recognized with ease radiologically. Awareness of its existence is of value to the surgeon in planning operation in cases of Fallot's tetralogy. Accurate identification of the vessels arising from the aortic arch is essential before performing an anastomosis between the subclavian and pulmonary arteries. The origin of the anomalous vessel on the medial side of the aortic arch may be difficult to see and it can be overlooked. Bahnson and Blalock (1950) record that in three cases operated on early in their series the aberrant artery was not recognized and the carotid artery was used with its greater operative risk. Blalock (1948) states the retro-œsophageal right subclavian artery may be used to provide a satisfactory anastomosis with the right pulmonary artery: in most patients he performed the anastomosis without disturbing

the position of the artery, but in some the artery was divided distally and then brought round to the left and anterior to the œsophagus before anastomosing it with the right pulmonary artery.

The anomalous vessel may be associated with types of congenital cardiovascular disease other than pulmonary stenosis. A patent ductus was present in three of the cases described by Brean and Neuhauser (1947). East (1932) reported its occurrence in a post-mortem specimen in combination with coarctation of the aorta.

Summary

The reported cases of an anomalous right subclavian artery are reviewed briefly.

Seven examples of this condition are reported, four of which were associated with Fallot's tetralogy. The barium swallow and angiocardiographic appearances in some of the cases are described.

Attention is drawn to the value of radiological recognition of this anomaly in patients with dysphagia and in cases where it is associated with Fallot's tetralogy.

I am much indebted to Dr. Evan Bedford and to Mr. T. Holmes Sellors for permission to publish details of the cases of Fallot's tetralogy and to Professor A. Kekwick, Mr. D. Patey and Mr. R. Vaughan Hudson for allowing me to give the clinical findings of their patients. I wish to thank Sir Harold Graham Hodgson for his interest and support. I am most grateful to Mr. Turney of the Photographic Department of the Middlesex Hospital for the photographic reproductions.

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THE INNERVATION OF THE HEART

BY

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Clinical and research workers are occasionally confronted by problems concerning cardiac innervation that may not be answered by the scanty details given in textbooks, and special articles usually deal with only one facet of the subject. A résumé of available information may therefore prove helpful.

The heart is innervated by both sympathetic and parasympathetic nerves, and afferents from the parietal pericardium are also conveyed through the intercostal and phrenic nerves. The autonomic nerves, like the somatic, are under the control of higher centres.

Higher Centres Controlling Visceral Activities

The idea that visceral functions are controlled by higher centres was expressed by Willis (1664), but despite many intervening suggestive observations Hughlings Jackson (1873–74) was the first to state clearly, as a result of his clinical and pathological observations, that visceral activities must be represented at various levels in the central nervous system. Until comparatively recently the cerebral cortex was regarded as of subsidiary or negligible importance in relation to the autonomic nervous system, but it is now recognized that there is both motor and sensory autonomic representation in the cortex, with overlapping and close integration of somatic, autonomic, and other cortical areas, a fact explaining the common association of somatic and visceral effects and the correlation between somatic, autonomic, and mental states. Evidence on these matters has been obtained mainly by comparative researches, and the observations reported by many workers on the autonomic effects produced by stimulation, section, or ablation of various parts of the brain and cord have been reviewed or evaluated by Spiegel (1932), Hoff (1940), Miller (1942), Gellhorn (1943), Bucy (1949), Walshe (1951), Cloake (1952), and others. They reveal how gradually the importance of the frontal cortex, hypothalamus, and brain stem in controlling visceral activities was established. Recently, information about autonomic representation in the human brain has begun to accumulate as a result of clinical, operative, and pathological observations (Penfield and Rasmussen, 1950; Meyer *et. al.*, 1947; Freeman and Watts, 1947, 1948; and Beck, 1950). These observations on the human brain tend to confirm in several respects the findings in animals, although the localization of centres, the pathways of the tracts involved, and the degree of response to stimulation are not always similar in man and animals. It can be stated, however, with reasonable certainty that the frontal lobes influence autonomic activities. This cortical participation in the control of visceral innervation is shared by subcortical centres in the hypothalamus, and perhaps in the corpus striatum and the anterior lobe of the cerebellum. These activities are correlated and integrated by two-way cortico-hypothalamic interconnections (Le Gros Clark, 1948; Le Gros Clark and Meyer 1950), directly or via relays in the thalamus. The hypothalamus in turn is linked to lower centres in the brain stem and spinal cord, such as the vagal nuclei and the cells in the lateral horns of grey matter in the cord, by tracts the exact course of which has not yet been determined precisely even in animals. Despite this, the existence of afferent and efferent pathways linking

the hypothalamus with lower centres in the brain stem and cord concerned with cardiovascular, respiratory, and other autonomic activities is undoubted.

Having stressed, albeit briefly, the importance of these higher centres in controlling autonomic activities, let us now consider the sources of the sympathetic and parasympathetic cardiac fibres.

The Sympathetic Contribution

The sympathetic fibres innervating the heart are the axons of cells located in the lateral (intermedio-lateral) grey columns of the upper 4–5 thoracic segments of the spinal cord. They are myelinated preganglionic fibres and they leave the cord in the ventral roots of the corresponding spinal nerves. They soon enter white rami communicantes passing to adjacent ganglia in the paravertebral sympathetic trunks. Some relay in these ganglia, but others run upwards in the trunks to the cervical ganglia before forming synapses with efferent or postganglionic neurons (Fig. 1). The postganglionic axons are unmyelinated or thinly myelinated, and those for the

Fig. 1.—Diagram showing connections of sympathetic cardiac nerves. From higher centres in cortex, hypothalamus, and brain stem to neurons in lateral grey column of upper 4–5 thoracic cord segments—heavy continuous lines. Preganglionic fibres from lateral columnar cells to cervical and upper thoracic sympathetic trunk ganglia—dotted lines. Postganglionic fibres from trunk ganglia to cardiac plexus—less heavy, continuous lines. The afferent pathways are not indicated.

heart run in the various cardiac branches of the sympathetic trunks. Thus in the sympathetic component of the autonomic nervous system the synapses between pre- and post-ganglionic neurons are often at considerable distances from the structure innervated, e.g. some of the cardiac postganglionic fibres arise in the superior cervical ganglia and are lengthy. By contrast parasympathetic postganglionic fibres are short.

The afferent cardiac fibres in the sympathetic nerves are the peripheral processes of cells lying in the dorsal root ganglia of the upper 4–5 thoracic spinal nerves and the central processes enter the cord through the corresponding dorsal nerve roots. There they form synapses with cells in

the posterior and lateral columns of grey matter and, like their somatic counterparts, they take part in the formation of reflex arcs and also transmit impulses to second relays of afferent neurons which convey information about visceral activities upwards to higher centres. In addition they give off collaterals which act as association fibres and assist in integrating activities in adjacent segments.

The Sympathetic Cardiac Branches. Three pairs of cardiac sympathetic nerves are derived from the cervical ganglia of the sympathetic trunks, and others come from the upper 4–5 thoracic ganglia (Fig. 2 and 3).

The superior cervical sympathetic cardiac nerve originates on each side from the lower part of the superior cervical ganglion or from the sympathetic trunk below it, and runs downwards near the trunk behind the carotid sheath. It usually unites with the corresponding vagal cardiac branches, and as the conjoined nerve descends it communicates through slender rami with the pharyngeal, laryngeal, carotid, thyroid, and recurrent laryngeal nerves. At the root of the neck it lies behind the subclavian artery. On the right side the nerve passes posterolateral to the innominate artery and aortic arch to the cardiac plexus: on the left side it lies in contact with the left common carotid artery and curves downwards across the left side of the aortic arch to the cardiac plexus. It always communicates with cardiac branches from the middle and inferior cervical sympathetic ganglia and occasionally unites with them or the corresponding vagal groups of cardiac nerves.

The middle cervical sympathetic cardiac nerve(s) is derived from the middle cervical ganglion or the adjacent part of the sympathetic trunk, and other filaments may be contributed to it by the vertebral ganglion (ganglion intermédiaire). It may proceed independently to the cardiac plexus, lying near and communicating with the superior sympathetic cardiac nerve, or it may coalesce with a vagal cardiac branch on one or both sides en route to the cardiac plexus. It is connected with the tracheal, œsophageal, and thyroid branches of the sympathetic trunks and is often the largest of the sympathetic cardiac nerves.

The inferior cervical sympathetic cardiac nerves consist of a variable number of filaments arising from the stellate ganglia and ansa subclavia, a single nerve being uncommon. They often combine with each other or with other cardiac nerves before entering the cardiac plexus, and inconstant twigs from them are sometimes attached to the delicate bundle of fibres connecting the phrenic nerve to the homolateral ansa subclavia.

The thoracic cardiac nerves (Fig. 3) consist of a variable number of filaments derived from the second to the fourth or occasionally fifth thoracic ganglia inclusive. When the first thoracic ganglion is not fused to the inferior cervical ganglion it also gives off a cardiac filament, but when a stellate ganglion is present (it exists in 75–80 per cent of human subjects) its inferior cardiac branches contain fibres from both ganglia.

The thoracic cardiac nerves run forwards and medially and some may enter the cardiac plexus directly, or they unite with neighbouring filaments destined for the trachea, œsophagus, aorta, or pulmonary structures and then separate again into their component elements as they approach the structures to be innervated; this can be shown by microdissection. The lowest thoracic cardiac filaments are interconnected with the upper rootlets of the para-aortic nerve (Mitchell, 1938, 1947).

Efferent accelerator and some afferent fibres from the heart and great vessels pass through these nerves, and because of their importance in the treatment of angina pectoris (White and White, 1928; Govaerts, 1936; White, 1940; Lindgren and Olivecrona, 1947; and White and Bland, 1948) they have aroused considerable interest. They were rediscovered comparatively recently (Braeucker, 1927; Ionesco and Enachescho, 1927), but as Mitchell (1949) showed, thoracic cardiac branches had been demonstrated at least one hundred years earlier by E. H. Weber (1815) in a calf and by Swan (1830) in man.

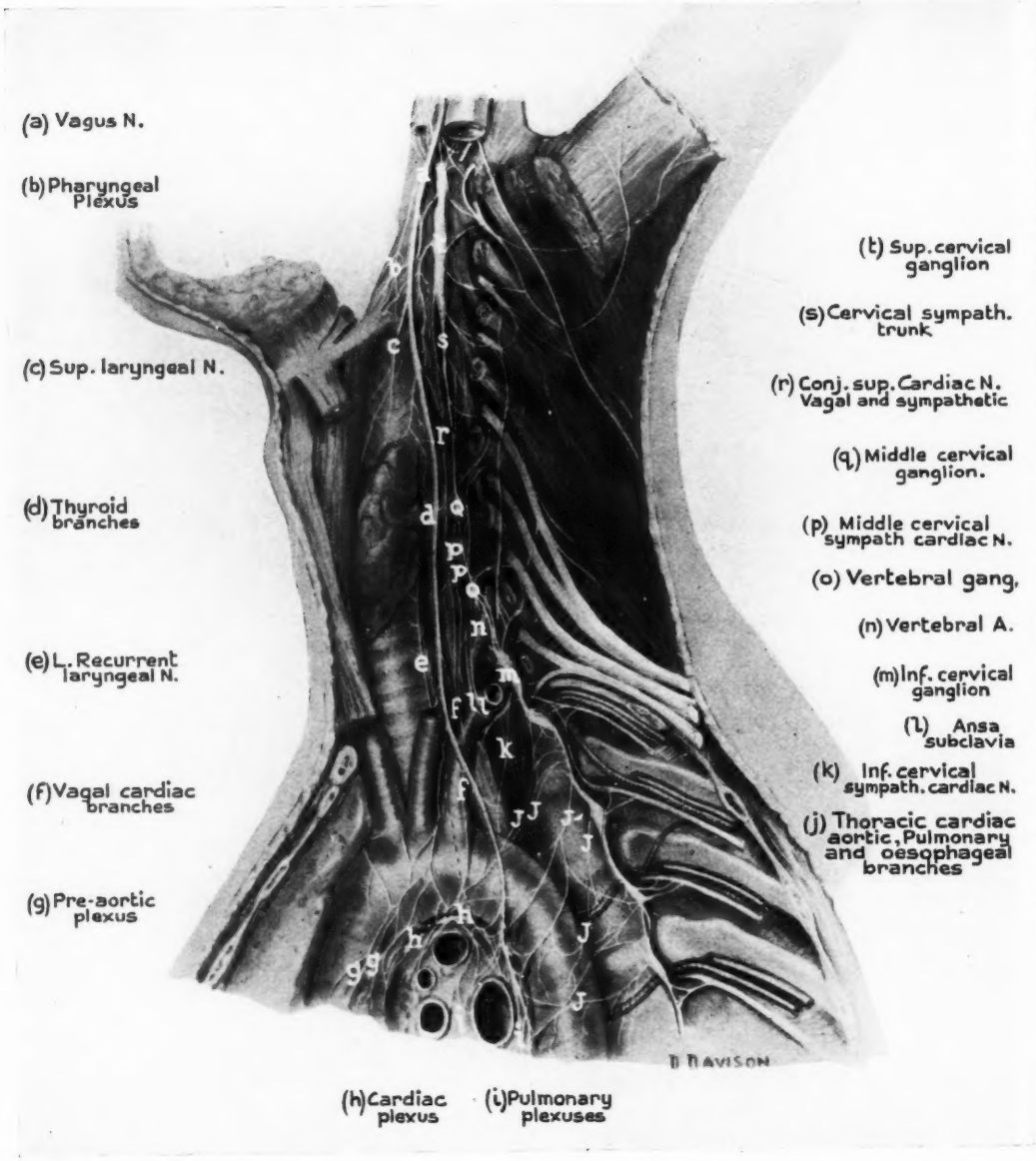
(a) Vagus N.
(b) Pharyngeal Plexus
(c) Sup. laryngeal N.
(d) Thyroid branches
(e) L. Recurrent laryngeal N.
(f) Vagal cardiac branches
(g) Pre-aortic plexus
(t) Sup. cervical ganglion
(s) Cervical sympath. trunk
(r) Conj. sup. Cardiac N. Vagal and sympathetic
(q) Middle cervical ganglion.
(p) Middle cervical sympath cardiac N.
(o) Vertebral gang.
(n) Vertebral A.
(m) Inf. cervical ganglion
(l) Ansa subclavia
(k) Inf. cervical sympath. cardiac N.
(j) Thoracic cardiac aortic, Pulmonary and oesophageal branches
(h) Cardiac plexus
(i) Pulmonary plexuses
DAVISON

FIG. 2.—The left side of the neck and upper thorax showing the main branches of the left sympathetic trunk and vagus nerve in these regions. To avoid overloading the picture many of the finer filaments, which cannot be seen clearly without the aid of a dissecting microscope, are not shown.

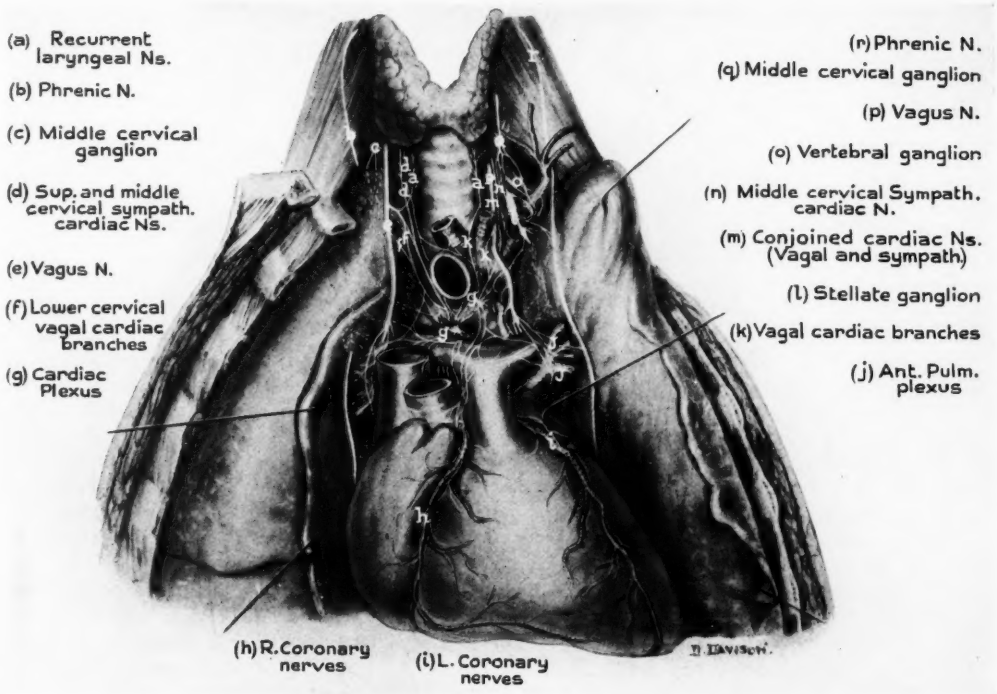
(a) Recurrent laryngeal Ns.
(b) Phrenic N.
(c) Middle cervical ganglion
(d) Sup. and middle cervical sympath. cardiac Ns.
(e) Vagus N.
(f) Lower cervical vagal cardiac branches
(g) Cardiac Plexus
(r) Phrenic N.
(q) Middle cervical ganglion
(p) Vagus N.
(o) Vertebral ganglion
(n) Middle cervical Sympath. cardiac N.
(m) Conjoined cardiac Ns. (Vagal and sympath)
(l) Stellate ganglion
(k) Vagal cardiac branches
(j) Ant. Pulm. plexus
(h) R. Coronary nerves
(i) L. Coronary nerves
H. Davison.

FIG. 3.—The root of the neck and thorax showing the chief cardiac sympathetic and parasympathetic branches and the cardiac plexus. The portions of the sympathetic trunks and their branches hidden by the lungs are indicated by dotted lines. Finer filaments which cannot be seen without a dissecting microscope are not indicated.

THE PARASYMPATHETIC CONTRIBUTION

The cardiac parasympathetic fibres are carried in the vagi and in the cranial parts of the accessory nerves that join them. The cardiac preganglionic fibres are myelinated and originate in the dorsal vagal nucleus and from a group of cells partially commingled with the nucleus ambiguus. Both these nuclei are elongated columns of cells lying in the medulla oblongata. The cardiac fibres are conveyed to their terminations in the vagus nerves and their branches, and they end by forming synapses with postganglionic neurons in ganglia in the cardiac plexus or in the wall of the heart. Synaptic relays close to or within the viscus supplied are characteristic of parasympathetic innervation and in consequence parasympathetic postganglionic fibres are relatively short compared with their sympathetic counterparts, and more circumscribed in their distribution. This is one reason why parasympathetic effects are more localized than sympathetic effects.

The dorsal vagal nuclei are of mixed type and represent fused efferent and afferent columns of neurons. The visceral afferents ending in these nuclei are the central processes of cells located in the inferior vagal (nodose) ganglia, situated on the vagus nerves just below the jugular foramina and the peripheral processes of these cells are distributed through the vagi and their branches to receptor endings in the heart, great vessels, and the many other structures supplied by these nerves.

After emerging from the skull through the jugular foramina each vagus nerve descends through the neck in the carotid sheath, lying behind and between the internal jugular vein and the internal and common carotid arteries.

The *right vagus* nerve enters the thorax by crossing the first part of the subclavian artery, behind the right internal jugular vein, and gives off its recurrent laryngeal branch. Descending posterior to the right innominate vein, it then inclines posteromedially behind the superior vena cava and medial to the vena azygos to reach the right side of the trachea and the root of the right lung. The *left vagus* nerve enters the thorax between the left common carotid and subclavian arteries, behind the corresponding innominate vein, descends across the left side of the aortic arch where it gives off its recurrent laryngeal branch, and then reaches the root of the left lung. The further course, connections, and distribution of these nerves need not be described here.

The Parasympathetic Cardiac Branches. These are variable in their size, number, and distribution, and arise from the vagi both in the neck and thorax (Fig. 2 and 3). The variability is apparent if one compares the descriptions and illustrations of these branches in the works of Walter (1783), Scarpa (1794), Swan (1830), Valentin (1843), Bourgery (1844), Hirschfeld and Leveille (1853), Schwalbe (1881), Sobotta and McMurrich (1907), Mollard (1908), Müller (1924), Braeucker (1927), Hovelacque (1927), Arnulf (1939, 1950), Hantz (1951), and many others, and one has confirmed it by personal observations. However, a general pattern is evident, and the cardiac branches may be divided into three groups—superior, middle, and inferior; all are interconnected at various levels with sympathetic branches, and sometimes with other nerves.

The superior vagal cardiac branches are two or three filaments which leave the vagus nerve in the upper part of the neck and after a short course they almost invariably join the homolateral superior cervical sympathetic cardiac nerve (p. 161). They often communicate with the vagal pharyngeal and laryngeal branches and occasionally with the carotid sinus and descendens cervicalis nerves.

The middle group consists of one to three branchlets arising in the lower third of the neck. They communicate with the sympathetic cardiac nerves and may unite with them, most commonly with those arising from the middle, vertebral, or inferior cervical ganglia. If they remain separate they pass directly to the cardiac plexus, lying posterolateral to the innominate artery and aortic arch on the right side, and lateral to the left common carotid artery and/or subclavian artery and aortic arch on the left side. Branches curve around the roots of the subclavian arteries, or on the right side around the innominate artery, to reach the anterior surface of the ascending aorta where they assist in the formation of the pre-aortic plexus.

The inferior vagal cardiac branches arise from the main nerve at the cervicothoracic inlet or within the upper thorax. Cardiac twigs from the right recurrent laryngeal nerve join one derived from the vagus nerve in the superior mediastinum, and this conjoint nerve may also unite with one or more thoracic cardiac sympathetic nerves before passing on the right side of the aortic arch to the cardiac plexus. On the left side one fairly large vagal branch usually detaches itself above the level of origin of the left subclavian artery and runs across the left side of the aortic arch to the cardiac plexus. In addition, the left recurrent laryngeal nerve and the parts of the vagus nearby invariably give off a number of filaments which end in the adjacent part of the cardiac plexus.

A few ganglion cells may be detected microscopically along the course of both sympathetic and parasympathetic cardiac nerves, becoming more numerous as the heart is approached.

The Cardiac Plexus

The various vagal and sympathetic cardiac nerves end in this plexus (Fig. 3) and in it they lose their individual identities, if they have not done so already through fusion with other nerves, although in some lower animals the right and left groups of nerves remain separate and are distributed mainly to the corresponding sides of the heart.

It is customary to describe the cardiac plexus as consisting of superficial (anterior) and deep (posterior) parts, and some have subdivided it still further. The superficial part, lying in the concavity of the aortic arch, usually receives the superior cervical sympathetic and inferior vagal cardiac nerves of the left side. The deep part, which lies behind the aortic arch and anterior to

the tracheal bifurcation, receives all the other vagal and sympathetic cardiac branches. Actually, subdivisions of this nature are artificial, as there is comparatively little difference between the depth of the so-called superficial and deep parts; besides, both are interconnected so freely that they may be regarded as a single unit, although some tendency to division into right and left halves is sometimes apparent, and from these the right and left coronary nerves mainly arise.

However, there is a more superficial part of the plexus lying anterior to the ascending aorta and termed the pre-aortic plexus (Arnulf, 1939, 1950). It is tenuous in nature and is formed mainly by filaments from the left vagal and sympathetic cardiac nerves, which incline forwards to reach the anterior surface of the ascending aorta (Fig. 2). It is always reinforced by a few twigs from the corresponding nerves of the right side, which curve around the innominate artery to join the plexus.

Several ganglia, in which a proportion of the vagal preganglionic fibres relay, are present in the plexus. The largest, the ganglion of Wrisberg (1800), usually lies below the aortic arch, between

FIG. 4.—Branching bundles of nerve fibres in subepicardium of left atrium (×90). The following details apply to all the photomicrographs reproduced, and will not be repeated in subsequent legends. Sections are from the rabbit and are stained with combined intravital and supravital methylene blue. The relative lack of background detail is explained by the fact that, owing to the thickness of the sections used, partial preliminary clearing in glycerine ammonium picrate was necessary before microscopy was possible.

the tracheal bifurcation and the division of the pulmonary trunk. Other minute parasympathetic ganglia are located in the wall of the heart, mainly in the atria and interatrial septum and in areas near the roots of the great vessels. These lie in the subepicardial tissue and are termed intrinsic

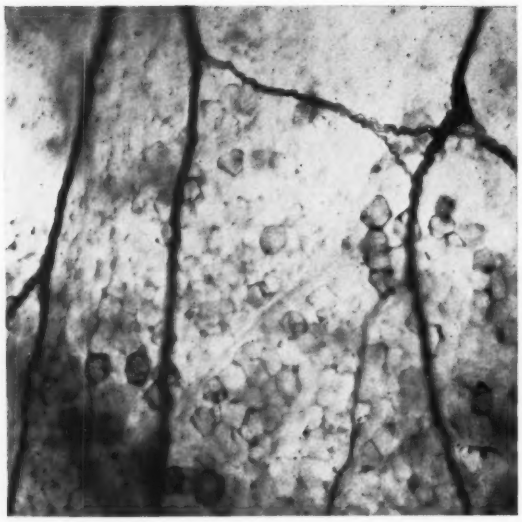

FIG. 5.—Nerve bundles branching in subepicardium of left ventricle (×140).

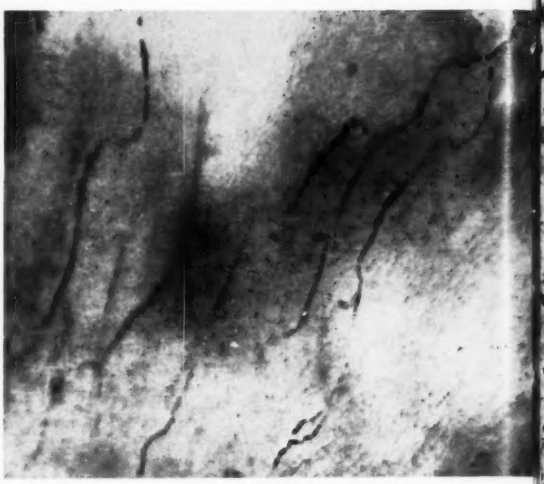

FIG. 6.—Network of nerve fibrils in myocardium (×625).

cardiac ganglia. In man and most mammals they are scarce or absent in the ventricles (Davies *et al.*, 1952).

Filaments from the right and left halves of the cardiac plexus converge towards the coronary arteries, forming subsidiary plexuses around them and sending offshoots along their various branches. Other slender twigs from the cardiac plexus pass directly to adjacent parts of the heart, pericardium, aorta, superior vena cava, and pulmonary vessels. The nerves lie initially in the subepicardial tissue and branch within it (Fig. 4 and 5), communicating with adjacent filaments through delicate strands. Some fibres innervate the vessels and epicardium, others penetrate and supply the myocardium (Fig. 6), and a number reach the subendocardial tissue where they unite with other similar fibres to form a fine network (Fig. 7). The fibrous pericardium (Fig. 8) is probably supplied chiefly by the phrenic and intercostal nerves and its sensitivity is of somatic rather than autonomic type.

CARDIAC AFFERENT AND EFFERENT NERVES

All the cardiac nerves contain both afferent and efferent fibres, with the exception of the branches derived from the superior cervical sympathetic ganglia which are believed to transmit only efferent fibres.

The idea of autonomic afferents may conflict with some preconceived notions, but many visceral fibres in sympathetic and parasympathetic nerves are afferents, and the conception of the autonomic nervous system as purely efferent is a misconception. There are no fundamental differences between the somatic and autonomic components of the nervous system in this or other respects. They originate from the same primordial cells, they develop together, they are built up from the same basic units or neurons associated in similar reflex arcs, they comprise central and peripheral parts, and structurally they are always related and often closely connected. Any separation, therefore, is artificial rather than fundamental, and is based chiefly on functional grounds.

Afferents. The afferent fibres are the processes of cells in the inferior vagal ganglia and in the dorsal root ganglia of the upper 4–5 thoracic spinal nerves. The central processes of the vagal

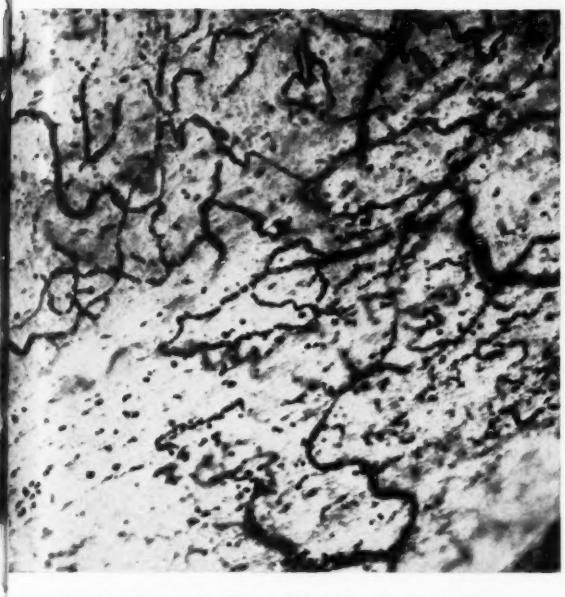

FIG. 7.—Network of nerve fibrils in subendocardium of infundibulum (×660).

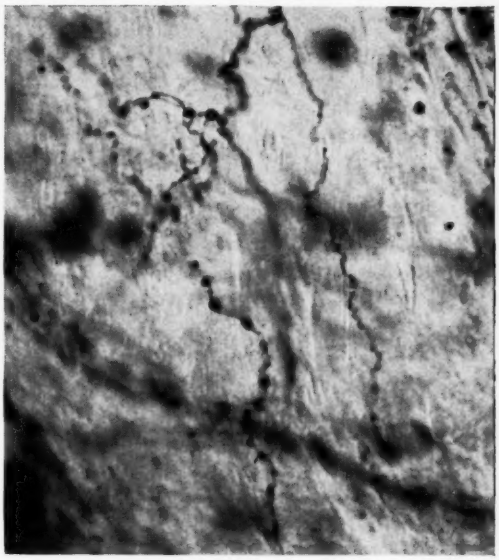

FIG. 8.—Beaded nerve fibrils in pericardium (×625). Reproduced by courtesy of Dr. E. P. Samuel, Manchester University.

fibres end mainly in the homolateral dorsal vagal nucleus, but others, or axon collaterals, end in the heterolateral nucleus, in the cardiac nucleus adjacent to the nucleus ambiguus, or in the grey matter of the formatio reticularis. The central processes of the spinal fibres end by forming synapses around cells in the posterior and lateral grey columns of the cord. One has mentioned already that both vagal and spinal fibres take part in the formation of reflex arcs, and that impulses are also carried upwards to higher levels in the brain stem, hypothalamus, thalamus, and cortex.

The peripheral processes of the cells in the vagal and dorsal root ganglia reach the heart and related structures through the cardiac branches of the vagi and sympathetic trunks and, thereafter, through the cardiac plexus and its offshoots. They do not relay in any of the extrinsic or intrinsic cardiac ganglia, but terminate in free endings, spirals, networks, and in other structures of a reputedly sensory nature, which are receptive to pain, stretch, pressure, chemical, and other stimuli. These are present in the subepicardium, between the cardiac muscle fibres, in the subendocardium, in the aortic arch bodies, and in the coronary arteries, aorta, and other great vessels passing to and from the heart. Many of the terminal nerve fibrils are beaded or varicose. The impulses originating in these structures are transmitted to the central nervous system via sympathetic and parasympathetic afferent fibres and are involved in cardiac and vasomotor regulatory mechanisms.

Many of the afferent vagal fibres from the heart and great vessels (Fig. 9) are concerned in reflexes that depress cardiac activity and in some animals they are aggregated in a separate vagal component, the depressor nerve (Cyon and Ludwig, 1866–67); in man these fibres may run in cardiac filaments of the vagal laryngeal nerves (Mollard, 1908).

Afferent pain fibres from the heart and aorta are conveyed mainly or entirely through the middle and inferior cervical and the thoracic sympathetic cardiac nerves, but those carried in the cervical nerves descend in the sympathetic trunks to the upper thoracic region, and all the fibres pass through rami communicantes to the upper 4–5 thoracic spinal nerves. Their cell stations are in the corresponding dorsal root ganglia, and the central processes of the cells enter the cord

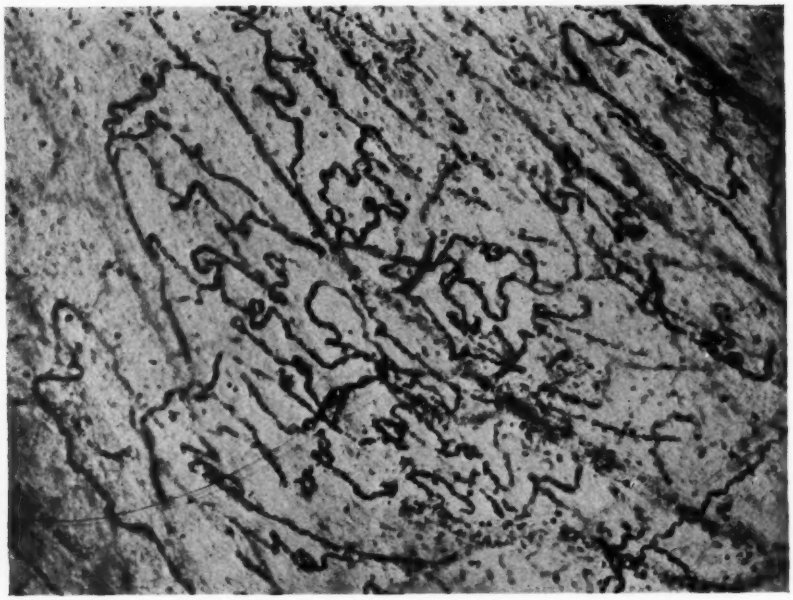

FIG. 9.—Nerve network in ascending aorta (×640), reputedly associated with the reception of impulses concerned in depressor activities.

through these dorsal nerve roots. This explains why in the treatment of angina pectoris attention is concentrated on the upper thoracic sympathetic trunk ganglia and rami, or on the corresponding dorsal spinal nerve roots. Interruption of these pathways by injection or operative techniques suppresses pain of cardiac origin, although in a minority of patients referred pains may still be experienced in the region of the ear and lower jaw; this is abolished by injection of the mandibular nerve (Lindgren and Olivecrona, 1947), but persists after destruction of the superior cervical sympathetic ganglion (White and Bland, 1948). Presumably the afferents involved in such cases travel in the vagi; incidentally thick myelinated vagal fibres of afferent type end in the adventitia of the coronary arteries. The dull sense of oppression felt during anginal attacks in the suprasternal and supraclavicular regions is not abolished by complete sympathetic denervation of the heart, and this suggests that some cardiac or vascular afferents are conveyed through the phrenic nerves. These nerves supply fibres that enter the pericardium, and the left phrenic nerve contributes a filament or filaments to the left anterior pulmonary plexus, which is closely interconnected with the cardiac plexus. Thus some phrenic fibres could easily reach the heart and great vessels, either directly or through the cardiac plexus. The phrenic nerves could also receive cardiac afferent fibres through other interconnections, such as those between them and the stellate ganglia and their ansæ, which also supply a group of cardiac nerves. There are other possible explanations of the persistent sense of oppression; a small proportion of the afferent fibres in the middle cervical sympathetic nerves may not descend to the thoracic region before entering the cord, but may enter it through the fifth, sixth, or seventh cervical nerves; or some afferents may travel upwards for a certain distance in the vagi and then pass through the constant communications that exist between them and adjacent branches of the cervical sympathetic ganglia.

Efferents. The parasympathetic cardiac preganglionic fibres arise on each side from a group of cells lying adjacent to the nucleus ambiguus and from the dorsal vagal nucleus. They are carried

in the vagus nerve and its cardiac branches to the cardiac plexus where a proportion of the fibres form synapses in its ganglia. Others proceed through the plexus and relay in the intrinsic cardiac ganglia. The postganglionic or efferent fibres reach the cardiac muscle and the unstriated fibres in the vessel walls through the various branches of the cardiac and coronary plexuses described above.

The sympathetic cardiac preganglionic fibres originate from cells in the lateral (intermediolateral) grey columns of the upper 4–5 thoracic spinal cord segments, and the representation is inverted, the ventricular fibres arising above those for the atria. They reach the sympathetic trunks through the white rami communicantes between the upper thoracic spinal nerves and corresponding ganglia of the sympathetic trunks. Some form synapses in these ganglia and others ascend to the cervical ganglia before relaying, and the postganglionic or efferent fibres are conveyed to the cardiac plexus in the various cervical and thoracic sympathetic cardiac nerves already described. They do not relay in the cardiac ganglia, but pass in the various branches of the cardiac and coronary plexuses to the structures they supply.

The atria, the sinu-atrial node, and the atrioventricular bundle are supplied by both vagal and sympathetic efferent fibres, and some of the fibres innervating the ventricles accompany this bundle. The available evidence suggests that the ventricular supply is predominantly although not entirely sympathetic, but the problem of whether conduction from the atria to the ventricles is myogenic, neurogenic, or a combination of both remains sub-judice, with the balance tilted in favour of the myogenic theory (Davies and Francis, 1952).

There is much argument about the exact mode of termination of autonomic efferent fibres in the heart and other visceral structures. A discussion of this problem is outside the scope of this communication. Suffice it to say that several observers have described small bulb and loop endings within the muscle fibres (Woollard, 1926), but others believe that the nerve fibres end by joining together in an extremely delicate terminal reticulum or syncitium (Fig. 10), while some go further and claim there is also a syncitial relationship between the terminal nerve fibres and the cells they innervate. This hypothesis has aroused much controversy, but if a terminal syncitium does exist in the autonomic nervous system, the neuron theory with its insistence on the anatomical discontinuity of all neurons and theories based on chemical mediation across hypothetical gaps will require revision. Eminent neurohistologists (Schabadash, 1930; Stöhr, 1932, 1950; Reiser, 1933; Boeke, 1940, 1949; Jabonero *et al.*, 1951; and Jabonero, 1952) have propounded the idea of a terminal reticulum in the autonomic nervous system, and in the case of the heart it has received

FIG. 10.—Terminal nerve network around arteriole (× 700).

support from the studies of Vitali (1937), Meyling (1948), Akkeringa (1949), and Field (1951). The syncitial conception has been criticized, amongst others, by Nonidez (1936, 1937, 1939 and 1943), Maximow and Bloom (1948), and Weddell and Zander (1951).

In general the vagal efferent impulses produce slowing or inhibition of the heart and constriction of the coronary arteries. The sympathetic efferents produce cardiac acceleration and coronary dilatation. The effects on the coronary vessels are the reverse of those produced by sympathetic and parasympathetic nerves on most other vessels, and functionally this is understandable because increased and decreased cardiac activity necessitate a greater and lesser blood flow respectively.

Summary

Visceral control by higher nervous centres is stressed.

The origins, pathways, and connections of the sympathetic and parasympathetic cardiac fibres are described.

Details are given of the sympathetic and vagal cardiac branches and of their communications with other nerves.

Information about the cardiac plexus, its ganglia and the mode of termination of its fibres is briefly reviewed.

The chief features of the cardiac afferents and efferents are epitomized.

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PAROXYSMAL VENTRICULAR TACHYCARDIA

A CLINICAL CLASSIFICATION

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The Lyonese school has been interested since 1920 in the subject of paroxysmal ventricular tachycardia. The excellent article by Armbrust and Levine (1950), based upon the study of one hundred cases, has encouraged us to attempt again to classify the different forms of this abnormal rhythm.

Although this disorder was identified in 1909 by Thomas Lewis it was Louis Gallavardin who, as early as 1920, described and emphasized the *terminal prefibrillatory ventricular tachycardia*, the extreme gravity of which he underlined by this very title. At the same time, he described the first clinical sign of ventricular paroxysms, namely the presence of a slow dissociated jugular pulse, a clinical proof of the independent auricular rhythm registered electrocardiographically. Soon after, in 1922, these severe forms were compared by him with a milder form of ventricular paroxysms: *ventricular extrasystoles with paroxysms of tachycardia.* About the same time others confirmed and extended these original descriptions. We may mention the studies of Robinson and Herrmann (1921) stressing the frequency of myocardial infarction as the precipitating cause of these ventricular paroxysms, and also the work of Dieuaide and Davidson (1921), of Gallemaerts (1923), and of Wolferth and McMillan (1923), which emphasized the remarkable therapeutic action of quinidine during such attacks. By this time, severe forms of ventricular tachycardia were well recognized and observations were reported from many quarters, but the milder forms still received little notice (Parkinson and Papp, 1947).

The study of paroxysmal ventricular tachycardia presented by Froment in 1932, and made under Gallavardin's direction constituted a step towards classification. In this work, based on personal observations and on an exhaustive survey of published cases up to that date, we distinguished the following varieties.

(1) Severe and terminal forms of ventricular tachycardia usually affecting patients with serious underlying heart disease.

(2) Ventricular extrasystoles with paroxysms of tachycardia, an essentially milder form affecting those with normal hearts.

(3) In contrast to the terminal forms that are nearly always mortal at short notice, what we then called *initial ventricular tachycardia*, sometimes due to myocardial infarction, and often of less immediate gravity.

(4) A less familiar group of important ventricular paroxysms developing in those with apparently sound hearts or hearts not greatly injured. We discussed the existence of this group, without expressing an opinion as to the prognosis. Since then, several large series of cases (Campbell, 1947; Herrmann and Hejtmancik, 1948; Armbrust and Levine, 1950; etc.) and many single cases have been reported, all of which have contributed to a clarification of the subject. The approach to ventricular tachycardia, at first electrocardiographic, is becoming more and more clinical and the existence of several distinct types has been confirmed.

The purpose of this paper is not so much to bring forward new facts, as *to propose a classification and an interpretation of the various forms of ventricular tachycardia based primarily on their different modes of evolution.* In this connection we shall refer to cases that we have observed which are noteworthy on account of particular features.

I. Terminal Prefibrillatory Ventricular Tachycardia

This type was the first to be recognized (Gallavardin, 1920). It is always associated with myocardial damage or exhaustion, and usually indicates that the end is drawing near. The clinical picture, the usual electrical polymorphism or alternance, and the frequent role of digitalis as a factor are too well known to need emphasis. These paroxysms do not seem to belong to any special ætiologic type of cardiopathy but, from a clinical point of view, they merely indicate the pre-terminal decline of an exhausted myocardium. We believe with Mahaim that damage to the conduction system is the predominant factor. Besides their great prognostic value, they are interesting because they are so often heralded by characteristic electrical prodromes (Gallavardin's prefibrillatory ventricular syndrome): these warnings indicate the need for discontinuing digitalis or at least for giving it with the utmost caution since it can easily aggravate the trouble.

II. Curable and Mild Monomorphic Ventricular Extrasystoles with Paroxysms of Tachycardia

This type is entirely different from the first and, since Gallavardin's original descriptions, its particular features, its benign course, and its curability have become well established. It is characterized by an almost permanent extrasystolic irregularity interspersed with paroxysms of tachycardia of brief duration; in severe forms these paroxysms tend to become longer and longer until they coalesce into prolonged attacks which are interrupted by sinus beats only at long intervals. This trouble specially affects young subjects with healthy hearts and, as a rule, it is very resistant to therapy, including quinidine.

The paroxysms are strictly monomorphic from an electrical point of view; the frequent isolated extrasystoles have the same contour as the beats that constitute the paroxysms. It is a rare functional disorder which may cause vertigo with alternating pallor and flushing of the face such as is seen in Stokes-Adams syndrome; more rarely faintness occurs at the onset, and still more rarely, episodes of transient heart failure occur when the attacks are unusually prolonged (Gallavardin). Yet the essentially benign character of these paroxysms is proved by their persistence over long periods, for example two of our cases were followed over periods of 35 and 24 years: in both the disorder proved perfectly benign and in both it was completely cured in spite of its initial severity.

Case 1. A woman was regularly observed from 33 to 64 years of age (1920–51) with ventricular extrasystoles and paroxysms of tachycardia: these were intense for the first 20 years, but gradually improved and almost completely disappeared during the last 15 or 20 years.

This case was originally published by Louis Gallavardin; further information was supplied by Froment (1932) and by Léon Gallavardin (1946). The patient was re-examined in 1951 when she was perfectly well and completely free from her trouble.

From 1915 to 1932 the rhythm disorder was very persistent with innumerable ventricular extrasystoles. During bad periods there were prolonged paroxysms of tachycardia lasting 5 to 30 days, with asystolic manifestations; they were of such intensity that the severe ascites wrongly led to a diagnosis of tuberculous peritonitis, and in our absence the patient was submitted to operation.

After 1932 the trouble diminished, the paroxysms became shorter and shorter, not exceeding ten seconds, and much less frequent. Since that time she has been working hard as a midwife in a hospital and in 1946 she only presented infrequent extrasystoles with occasional paroxysms. At present she is in excellent health and leads an active life for a 64-year-old woman.

The cardiovascular examination between attacks showed nothing abnormal; in 1946 her blood pressure was 130/80 mm., the size of the heart was normal, and so was the electrocardiogram except for infrequent ventricular extrasystoles similar to the more numerous ones presented before. In 1951, there was no longer any disturbance of rhythm or any sign of heart failure.

Case 2. A man was under observation from 17 to 41 years of age (1927–51) with ventricular extrasystoles and paroxysms of tachycardia, at first of great intensity, but completely disappearing for the last 20 years.

This case was originally recorded by Gallavardin and Veil (1929), and later by Froment (1932; obs. II) and by Gallavardin (1946; obs. I). When seen again in 1951, he was absolutely normal from a cardiovascular point of view.

From 1927 to 1931 he was extremely uncomfortable with innumerable extrasystolic paroxysms which were badly tolerated. Every paroxysm lasting more than 3 or 4 seconds caused faintness with facial pallor, and once with loss of consciousness. In bad periods, paroxysms were almost continuous to the point that he had to abandon his studies. In better periods there were frequent extrasystoles similar in form to those of the paroxysms.

After 1932, the trouble gradually improved and the patient was able to lead a normal life; he fought in 1939 and spent 30 months as a prisoner of war, with very little trouble. He was re-examined in 1946 and again in 1951, when he was perfectly well and free from extrasystoles. Cardiac examination was normal, the blood pressure was 140/80 mm., radioscopy showed that the size of the heart was normal, and the electrocardiogram was also normal.

These two clinical reports testify to the benignity of this rhythm disorder. Though it had been severe in both, the ectopic rhythm disappeared completely and, after many years, they are free from all signs of failure. Therefore, neither the duration nor the repetition of the ventricular paroxysms constitutes an element of gravity. What seems to be important is the general myocardial integrity in young subjects who are capable of tolerating the most frequent paroxysms. It is likely that such rhythm disorders are caused by microscopic myocardial injury, probably of the bundle of His, acting as an *épine irritative*. The effect of this may gradually lessen on account of its evolution, or of change in the patient's neuro-vegetative condition as he grew older.

III. Paroxysmal Ventricular Tachycardia due to a Lesion of the Ventricular Septum

Since the original paper of Robinson and Herrmann (1921) showing the frequency of septal infarction in ventricular tachycardia, this special form has become well known. The work of Levine (1927) alone and with Fulton (1929) and Stevens (1927) contributed to establish its clinical features and therapy. Appearing at or closely following the clinical onset of cardiac infarction it may rarely be the only sign of this and, especially in elderly patients, it is always suggestive. The appearance of ventricular tachycardia on the occasion of a cardiac infarct is a serious danger, with the risk of heart failure and sudden death from ventricular fibrillation. However, thanks to quinidine, which is the fundamental drug in such cases, there may be important remissions even after long and recurrent attacks which seemed to be serious (5 years in a case of Bérard (1940); 11 years in one of Armbrust and Levine). The possibility of recovery is explained by a regression of the infarcted area responsible for the attacks.

Exceptionally, ventricular tachycardia is related to a syphilitic lesion of the septum. Cossio *et al.* (1937), reported the first example of it; at necropsy treponema were found in the septal gummatous lesions. Coelho and d'Oliveira (1939) published a similar case, also fatal. A patient whom we observed (Froment *et. al.*, 1944) recovered after intensive treatment and has kept free from paroxysms for the last seven years; his heart now appears normal. The following is a brief report of this case.

Case 3. A man, aged 46, apparently in good health, suffered in 1944 six attacks of paroxysmal ventricular tachycardia within a few weeks, the longest lasting 7 days. Bordet-Wassermann, Kahn, and Meinicke reactions were strongly positive. The attacks yielded readily to an intravenous injection of quinidine. From the start of anti-syphilitic treatment the attacks became progressively less frequent and of shorter duration. After 3 months the patient was well, having had only one very short attack; the serologic tests for syphilis were negative. Seen again in 1951, he was in good health and quite free from paroxysms of tachycardia. Clinical, radioscopic and electrocardiographic examinations show no cardiac abnormality now and serologic tests are negative.

A possible syphilitic origin of ventricular tachycardia, however exceptional, should be in mind, otherwise the advantage of specific treatment may be missed.

IV. Persistent and Prolonged Ventricular Tachycardia Developing in Sound Hearts Usually in Young Subjects

Besides the disorders of rhythm described, there are others that do not fit into the previous classification. These relate to prolonged ventricular paroxysms without any break, analogous, at least clinically, to the common paroxysms of the supraventricular tachycardia, though their ventricular origin is proved by the electrocardiogram. They are by no means a prefibrillatory type of ventricular tachycardia for they have neither the poor prognosis nor the cardiographic characteristics of it. They do not conform to the extrasystolic form with long runs of extrasystoles as there are neither isolated extrasystoles nor any short runs. On the contrary, paroxysms always have a massive and well-defined aspect. A vascular origin is very unlikely in young subjects who are often involved.

In 1932, we postulated a ventricular form of paroxysmal tachycardia with sharply defined paroxysms, affecting subjects with apparently healthy hearts, and running a benign course. Unquestionably, prolonged paroxysms of ventricular tachycardia do occur in patients with sound hearts, but can we expect the same benign course as occurs in the ordinary case of paroxysmal auricular tachycardia? It is difficult to be sure as the only irrefutable proof of benignity is the test of time. In this connection, we may cite a case which we have followed for a period of 11 years, and we may also cite reports by Bjerkelund (1949), Stein and Driscol (1947), Freunlich (1946), MacMillan and Bellet (1931), Campbell (1942), Clerc *et al.* (1933), Gaquière and Robin (1947), Peters and Penner (1946), Joly (1927), Donzelot *et al.* (1945), and Smith (1946).

Case 4. A man was observed from the age of 49 to 60 years (1939–50) during which he had over 400 attacks of ventricular tachycardia, usually lasting several days, and often requiring for an interruption an intravenous injection of quinidine. There was no sign of cardiopathy. In December, 1951, after the electrocardiogram was strictly normal, he was still subject to milder attacks.

D. . . . has been regularly observed by Dr. Bérard of St. Etienne since 1939, since which date he has been seen on several occasions by ourselves. He is apparently in good health except for an old healed lesion of the right lung, probably tuberculous. A benign diabetes mellitus has disappeared without having been treated. This man had led a normal life up to 1939, when at the age of 49 he began to have paroxysms of tachycardia at a rate 300 a minute, starting and ending abruptly. These attacks lasted from a few hours up to several days; the more prolonged ones led to a lipothymic state and forced the patient to rest. The frequency of the attacks varied from time to time; often he had several a month, sometimes several in the same week. These paroxysms were treated by injections of quinidine when they lasted more than two or three days. In 1942, we recognized their ventricular origin and noticed a very distinct dissociation of the jugular pulse.

In 1944, the attacks accurred far more frequently almost every day, and sometimes lasted as long as five days. Quinidine was always effective but it did not prevent the attacks. Five stellate-ganglion blocks gave no result. This state persisted during 1945 and 1946, though with better periods that could not be attributed to therapy.

In 1947 the patient called in a colleague who tried thoracic radiotherapy, an appendicectomy, and lastly a hemithyroidectomy, without success. Soon after the thyroid operation unexplained anasarca developed without cardiac signs and without relation to any prolonged attack; this cleared up within a month and never recurred.

In 1948 and 1949 he was still having frequent attacks. Since June, 1950, they have become shorter, lasting only one hour and less frequent; furthermore, oral quinidine has acted satisfactorily.

Cardiac examination between the attacks was always negative. There was no sign of heart failure apart from the unexplained anasarca following thyroidectomy. When last seen in 1950 there was regular sinus rhythm; radioscopy showed a heart of normal size; blood pressure was 100/70 mm. Hg; the cardiogram was normal, the electrical axis of QRS being $+80^{\circ}$. During the attacks, it shows a typical ventricular tachycardia, rate 200 to 210, with a dissociated auricular rhythm in lead II; there is post-paroxysmal inversion of T waves in leads II and III.

Comment. This case is a typical example of the ventricular form of Bouveret's disease. The paroxysms start and end suddenly, their frequent repetition rendered the patient an invalid at times and, finally, after 400 attacks during a period of eleven years, the heart remains intact. As the trouble started at the age of 49 a slight vascular lesion cannot be excluded, but such a benign course could not have been forseen when the attacks first occurred.

Case 5. A young man of 21 presented in two years and a half about thirty paroxysms of ventricular tachycardia lasting up to 24 days and always well tolerated. Cardiac examination was negative.

He had always been in good health, and worked as a craftsman without any fatigue, and had played games such as football. In June, 1948, he complained of feeling tired and of right subcostal discomfort, and we found a regular tachycardia at 170, of which the patient was unaware. After many therapeutic failures (intravenous acethycholine, oral quinicardine, and dilvasene) an intravenous injection of quinidine put an end to the attack. Levine's sign had been noticed, with obvious irregularities in the intensity of the first sound. In August, 1948, several slight attacks lasting 2 or 3 days were terminated by oral quinidine.

In September, another attack began and continued for twenty-four days without interruption. The cardiograms showed a typical ventricular tachycardia, rate 174. The electrical axis was at $+90°$ and the dissociated auricular rhythm was well seen in lead II. Variability of the first sound and jugular dissociation were obvious. All treatment, including intravenous quinidine was ineffective until the attack came to an end soon after administration of 1·2 g. of oral quinidine in four hours. During this attack, there was a very remarkable dilatation of the heart that receded within a week and a post-critical diastolic gallop which disappeared a few days later. Finally, we recorded typical post-paroxysmal cardiographic anomalies, namely flattening of T in lead I and deep inversion of T in V4, both of which disappeared within ten days. In the next three months, the patient had many short attacks, which were checked by oral quinidine. At the end of December, three days after an attack, there was slight dilatation of the heart and a normal cardiogram except for a flattened TI.

During 1949 and 1950, the patient had about one attack monthly, usually lasting a few hours, but was able to lead a normal life. Examination of the heart was negative between the attacks, the blood pressure being 12070 mm. and the cardiogram being normal. In November, 1950, he was reported as having only occasional attacks, and as leading an entirely normal life.

Case 6 (Dr. Froment and Trocmé). A 19-year-old man was in good health when, in June, 1947, while bathing, he presented a sudden ventricular paroxysm, rate 232. The attack lasted four days and came to an end after 1·2 g. of quinidine by mouth; shortly before the end of the attack, the rate fell to 192, and frequency of micturition occurred. The cardiogram showed a typical ventricular tachycardia, though the auricular rhythm was not evident. During the paroxysms, the electrical axis was at $+30°$. There were post-paroxysmal changes, namely, flattening of the T wave in lead I and considerable lengthening of the Q–T interval (0·56 secs.) which disappeared within ten days. Clinical and radiological examination showed that the heart was normal. In January, 1951, three and a half years later, the patient is reported to be leading a normal life, free from paroxysms.

This form of arrythmia consists of major paroxysms of ventricular tachycardia in subjects with apparently healthy hearts, and follows a favourable course even when of long duration. From the clinical standpoint, this ectopic rhythm resembles the common form of auricular paroxysmal tachycardia, and it may continue a favourable course for ten years or longer.

The age of onset of the paroxysms is variable, but is commonly around 20 years. Men predominate, the sex ratio being ten men to three women. The onset and offset of the paroxysms are well defined, as in ordinary paroxysmal tachycardia and the rate is high (159 to 243), but the duration of the attacks is noticeably longer, an important point of difference. Attacks lasting several days are the rule, and a duration of a week or longer is not uncommon, being observed in four out of ten cases. In paroxysmal atrial tachycardia, especially at the start, the attacks are usually shorter, for in 177 cases only 8 per cent of the attacks lasted longer than 5 days (Gallavardin and Froment, 1930). Finally, the paroxysms are usually well tolerated, rarely provoking faintness or heart failure which, if they occur, are nearly always in the more prolonged attacks.

Electrocardiographic changes are very common after paroxysms of this form of ventricular tachycardia. They have been much studied in recent years, especially by Cossio *et al.* (1944) who investigated them in 26 cases. Two main types of post-paroxysmal cardiographic change are

recognized, namely type TI (and TII), and type TIII (and TII). Type TI follows paroxysms in which there is a right electrical axis, and type TIII those with a left electrical axis, this rule applying to about two-thirds of cases. These important and often long-lasting changes in the cardiogram (lasting up to 54 days in a case reported by Smith, 1946) do not correspond to any serious myocardial damage for the lesion could scarcely recur in identical form after successive attacks. In two such cases examined at necropsy by Cossio, no macroscopic lesion was found. Experience shows that the occurrence of these post-paroxysmal electrical changes does not warrant a bad prognosis. Our case observed for 11 years presented gross changes of this type yet there were no serious consequences.

The origin of these ventricular paroxysms still remains a mystery. Our knowledge of cardiac physiology leads us to postulate the existence of an irritable focus in the septum, and probably a histological lesion of the conducting system that does not impair the functioning of the heart, so that the attacks are well tolerated. It is neither the long duration of the attacks nor their ventricular origin that is serious, but the deep septal lesion. In some cases, this lesion may be microscopic and without any effect on the functioning of the heart.

Summary

From personal observations and from a survey of reported cases, a clinical classification of the different forms of paroxysmal ventricular tachycardia is proposed as follows.

(1) Terminal prefibrillatory ventricular tachycardia (Gallavardin, 1920) usually complicating serious heart disease.

(2) Ventricular extrasystoles with paroxysms of tachycardia, a less serious form usually affecting healthy hearts.

(3) Ventricular paroxysmal tachycardia due to a serious septal lesion, especially septal infarction, and rarely a septal syphilitic lesion.

(4) Major paroxysms of ventricular tachycardia occurring usually in young subjects with apparently healthy hearts. This form resembles clinically the common paroxysmal auricular tachycardia. The clinical course may remain favourable even for ten years or longer. It is suggested that this disorder results from a microscopic lesion which is without effect on the functioning of the heart.

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CONGENITAL AORTIC VALVULAR STENOSIS

BY

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The frequency with which the diagnosis of aortic stenosis is missed has been increasingly realized during the last 25 years. When a rough systolic is heard at the base of the heart a special effort should be made to feel a thrill, and if these two signs are present the diagnosis of aortic stenosis must be considered. The presence or absence of peripheral signs in the pulse is merely a measure of the severity of the stenosis; this principle is more widely recognized when there is an aortic diastolic murmur and aortic regurgitation, and may or may not be a water-hammer pulse and a wide pulse pressure.

Ætiologically, there is an even greater neglect of a possible congenital origin. We think that congenital aortic stenosis is relatively common but is often missed because so many years may pass before there are significant symptoms, and in a patient of forty or so, the lesion is looked on as calcific or atheromatous when these changes are simple additions to the congenital lesion. This assessment is of more than academic interest, bearing both on prognosis and the consideration of surgical relief.

In this paper we wish to describe 40 cases of aortic stenosis that are, we think, congenital. About half of these were sent up ostensibly as congenital heart disease for a more detailed diagnosis, but nearly half were seen in routine cardiological practice and the possibility of the lesion being congenital had rarely been entertained.

The earliest description of aortic valvular stenosis is probably that of Carolus Rayger (1672), recorded by Bonetus (1679) in his "Sepulchretum," under the heading "de morte repentina." The observation was in a middle-aged Parisian cobbler who dropped dead in the street, and at necropsy showed aortic valves of "bone." Chevers (1842) recorded one variety in which the mouth of the aorta was contracted from birth, its valves being blended with each other so as to present a mere funnel-shaped tube with a slit at the apex.

Although the bulbus cordis forms a functionally important part of the outflow tract of the right ventricle, it is as a rule completely incorporated into the outflow tract of the left ventricle; if involution is incomplete a remnant persists in the form of a ridge or diaphragm containing elastic tissue, between the ventricular chamber and the aortic valves (Keith, 1924). Subaortic stenosis is understandable embryologically and is comparable with pulmonary infundibular stenosis, but the origin of aortic valvular stenosis is less obvious. The valves originate from division of the four bulbar cushions and faulty division may result in bicuspid valves. Koletsky (1941) refers to two types of this abnormality—one with two cusps that appear normal, and the other with one of the cusps divided by a narrow ridge of elastic tissue extending into the sinus in the long axis of the aorta. Where fusion and thickening of the aortic valves are present at birth, "fœtal endocarditis" has sometimes been invoked, and Brown (1950) inclines to this view. There are, however, many arguments against it, especially the resemblance to pulmonary valvular stenosis and the association with other congenital lesions, for example, the cases of Smart (1904) and Shennan (1905) with both valvular and subvalvular stenosis, and two of our own cases with dextrocardia.

Whatever the cause may be, the deformity progresses with the deposition of platelet thrombi and calcium until the original structure is buried in the calcified fibroid plaques, and the natural bias is to accept an acquired rheumatic ætiology. It is difficult to explain the rarity of calcification in stenosis of the pulmonary valve, whereas that of the aortic valve may be remarkably extensive (Fig. 1), unless perhaps patients with severe pulmonary stenosis do not live long enough.

FIG. 1.—Extensive calcification of the aortic valves and surrounding area from a young man, aged 18, with congenital aortic stenosis. Right anterior oblique view. Case 26. His sudden death after this paper was completed confirmed the diagnosis and the gross calcification.

CLINICAL FINDINGS

The table (see p. 187), with the patients arranged according to the age at which the murmur was first heard, gives some details of the findings. The physique of these patients is in the main outstandingly good as in many of those with coarctation of the aorta, and the delicate-looking gracile type is unusual. The sex incidence is striking, for there are no less than 31 males (77%). Karsner and Koletsky (1947), in reviewing aortic stenosis confirmed by necropsy, give the corrected incidence as three men to two women. In the present group there is no question of heavy manual

labour being a factor, for most of the hearts were recognized as abnormal before this could have been operative. The ages range from 3 to 50 years.

Age when Murmur was first Heard. This is important because the diagnosis of heart disease soon after birth is one of the best reasons for accepting it as congenital. There were 20 patients where the murmur was heard or the diagnosis was made in early childhood, sometimes in the first few months of life and generally before they were three years old, but twice in the fourth and twice in the fifth year. Most of these are still under ten, but there are two in their teens and six, five of whom are women, who are in good health at 24, 25, 34, 37, 38, and 38 years. Incidentally, two of the latter have recently been through a pregnancy without difficulty.

The development of a rheumatic valvular lesion before the age of three or four is so uncommon that it seems certain that these patients have congenital heart disease or, if not, are suffering from some infection that is not recognized as a cause of valvular disease.

There were another 17 patients, eight under 19 and nine between 23 and 50 years of age, where the murmur was heard later than this but while they were still children. It was heard before they were 11 in twelve, between 12 and 15 in three, and between 18 and 19 in two. The fifteen adults in these two groups are specially interesting when considering the prognosis of congenital aortic stenosis. There seems little doubt about most of these 37, but we are including three others (Cases 38, 39, and 40), as examples of older cases that are usually diagnosed as calcific aortic stenosis and not recognized as congenital. In these three—all men between 40 and 42—the murmur had only been heard a few years before, and sometimes it seemed that it should have been heard earlier at army examination or elsewhere if it had been present. It is possible that they have developed atherosclerosis on a valve that was normal, but they show no other evidence of this, and we think it more likely that aortic stenosis was present throughout life but gave rise to no symptoms until the development of sclerotic changes.

We have not included a doctor, aged 61, who has had a successful valvotomy for severe aortic stenosis, which may have been congenital as he had had a murmur and thrill, a low blood pressure, and a tendency to faintness for 35 years. As there was severe aortic stenosis without regurgitation or any evidence of mitral stenosis or much enlargement of the heart, it seems unlikely that it was rheumatic.

There was a history of rheumatic fever in two patients and a doubtful history in three more, but except in one (Case 28) this was later than the recognition of the murmur. None of them had any evidence of mitral stenosis, and the course in those who were observed for several years showed none of the special features of rheumatic heart disease.

The original diagnoses included ventricular septal defect in eight patients, congenital pulmonary stenosis in five, congenital aortic stenosis in four, patent ductus arteriosus in four, and rheumatic aortic incompetence in one.

Symptoms. The degree and onset of dyspnœa were variable; there were only nine patients in whom it was more than slight and then usually after the age of 30 years. Case 12 had in fact attended hospital at 16 years of age, as he wished to take part in cross-country running and 100-mile bicycle races, by neither of which he was unduly inconvenienced: his cardiogram (Fig. 2) showed gross left ventricular strain; but at the age of five it had shown some right axis deviation in the standard leads.

There were 11 instances of angina of effort, usually starting in the late teens; but none where it was present at rest. Eight patients complained of dizziness with effort, and more rarely of syncope: in three of these there was not concurrent angina of effort. About half these patients had a low pulse pressure around 20 mm. Hg, but it was equally small in as many of the others. Syncopal attacks with effort occurred in Case 7 when her hæmoglobin was 40 per cent, but were absent when it had risen to 80 per cent.

Signs. The pulse was often small and the pulse pressure was generally between 20–40 (average 31 mm. Hg). It was at the low level of about 15–25 in seventeen patients and generally there was more depression of the systolic level than elevation of the diastolic level. The pulse was recorded

as small in eight patients, as slow rising in five, as bisferiens in one, and as having some collapsing element in three, but even in these the pulse pressure was not wide. There is no reason for expecting a small pulse pressure in every case with aortic stenosis for the aortic orifice must be reduced to a quarter of its size before changes in the circulation can be demonstrated (Wiggers, 1935).

A left ventricular impulse was felt in half. It is notable that a systolic thrill was felt at some time in all patients, although its situation varied. In some it was palpable only above the sternal notch; in a child of three years (Case 8), it was felt at the apex only. The intensity of the thrill was

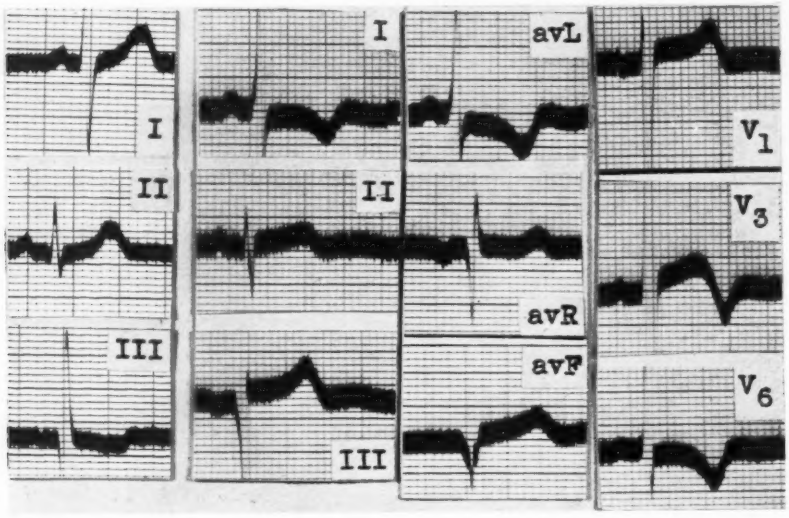

FIG. 2.—Electrocardiograms showing the development of left ventricular preponderance and strain. Case 12. (A) When aged 5, with some right axis deviation. (B) When aged 16, with left ventricular strain.

on occasion striking; in a girl, aged 8 (Case 22), it was felt through no less than 32 layers of thin blanket and in one woman (Case 18) its rasping quality interfered with sleep.

Systolic murmurs were invariably harsh, often conducted to the carotids, and heard principally at the base, but to this there were exceptions; in Case 35, at the age of 15, the murmur was found at the apex alone, but two years later it is well heard over the aortic area.

The aortic second sound was weak or absent in half the patients (19). In six of these the valves were seen to be calcified, but in the remainder with calcified valves the second sound was normal or even loud.

There were 18 patients with early diastolic murmurs, but in most of these it was a soft murmur that was not very easily heard, and there were only five in whom it was loud. The youngest was four (Case 3), yet in a number over 30 years of age diastolic murmurs were persistently absent (Case 37, aged 49). Case 9 apparently developed a diastolic murmur between four and six years of age.

In two instances (Cases 10 and 13) the heart lay mostly to the right of the midline.

Size and Shape of the Heart. Generally the heart was little enlarged, and this agrees with the classical view that aortic stenosis produces concentric hypertrophy, which is not easily seen, and that dilatation follows much later, if at all. In most of these patients the shape was normal or rather vertical, sometimes with obvious rounding of the left ventricle (Fig. 3–5); but in about one-sixth of

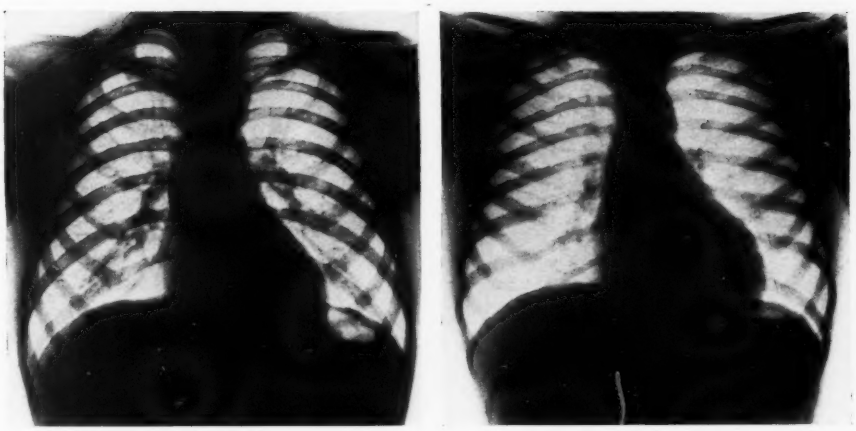

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FIG. 3.—The heart in children with congenital aortic stenosis, showing prominence of the first part of the aorta, but less than in some children and most older patients. (A) A small heart (c.t.r. 46%) from a boy, aged 12. Case 31. (B) A normal-sized heart (c.t.r. 50%) from a boy, aged 9. Case 11.

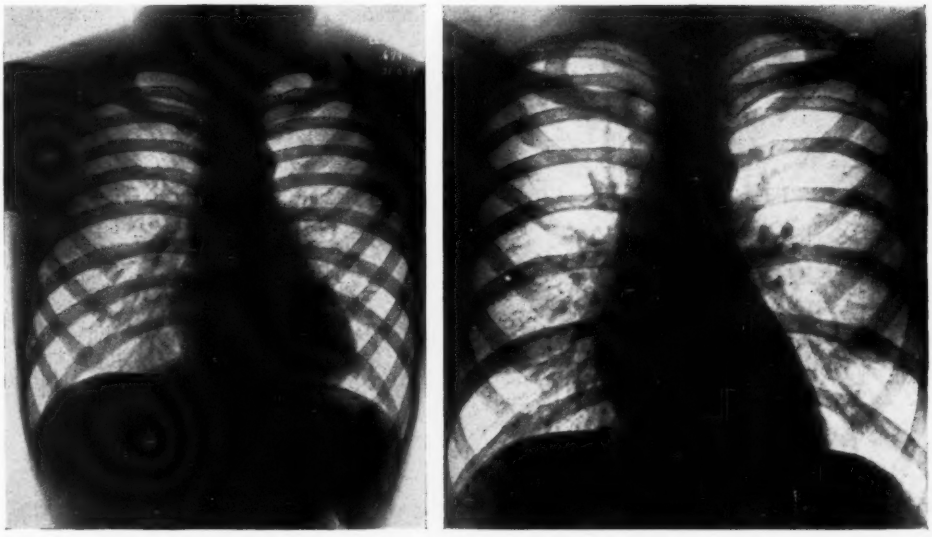

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FIG. 4.—The heart in congenital aortic stenosis, showing typical dilatation of the first part of the aorta. (A) From a girl, aged 9 (c.t.r. 49%). Case 21. (B) From a boy, aged 18 (c.t.r. 49%). Case 24.

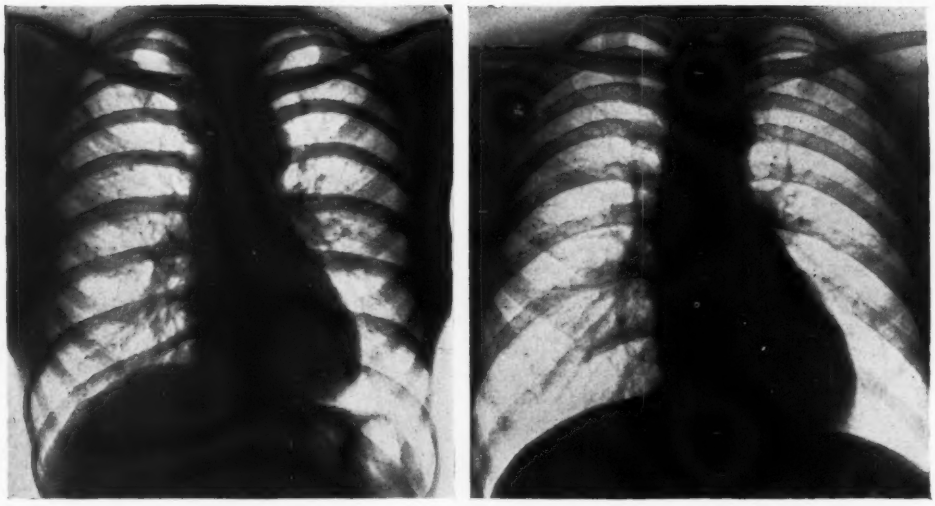

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FIG. 5.— The heart in congenital aortic stenosis in adults, still without cardiac enlargement. (A) From a man, aged 26 (c.t.r. 45%). Case 28. (B) From a woman, aged 37 (c.t.r. 46%). Case 7.

them the heart was larger than this and showed some tendency to become horizontal, thus resembling more closely the characteristic picture of aortic disease with incompetence (Fig. 6B and 7A).

Even on the film the dilatation of the first part of the aorta was noticeable in two-thirds of the patients, but in the remaining third the aorta looked normal. There were only two older patients with the general dilatation that is so often seen with atheroma. The aortic knuckle was not specially prominent as it so often is with an atheromatous aorta: it looked normal in about two-thirds of our patients, and was less visible than usual in the other third.

The cardiothoracic ratio was between 45 and 52 in two-thirds, and between 54 and 56 per cent in one-third of the patients. Rather surprisingly, the heart is not necessarily larger in the older patients, though this must certainly happen sometimes. If our cases are divided into three groups according to age, the average ratio was only a fraction above 50 per cent in each. The characteristic outline is seen again and again and the figures shown could have been reproduced almost exactly from other cases.

On fluoroscopy some enlargement of the left ventricle was almost invariable, but it was gross in only three (Cases 3, 36, and 37), and in retrospect it seems likely that the first of these had a ruptured aneurysm of the aortic sinus. The most striking and constant finding was the enlargement of the first part of the aorta, well shown in most of the figures and best seen on fluoroscopy in the left anterior oblique position. Fig. 7B illustrates a gross example, in which dilatation was such as to cause an impulse and pain in the right chest anteriorly. This dilatation and the hyperdynamic appearance were commented upon in almost all those over the age of ten years: they were not always associated with a diastolic murmur and only in Case 29 with a wide pulse pressure.

The aortic valves were seen to be calcified in 11 patients, such calcification extending at times beyond the cusps. In 7 of these 11 an early diastolic murmur was heard. The youngest in whom calcification was seen was 18 years of age (Case 26), and he was the only one of the twenty-three patients under 24 in whom it was seen. On the other hand it was seen in ten of the seventeen over 24 years of age. No special methods were used to demonstrate it, e.g. tomography, which Davies and Steiner (1949) thought the most effective. It was, therefore, probably present more often than

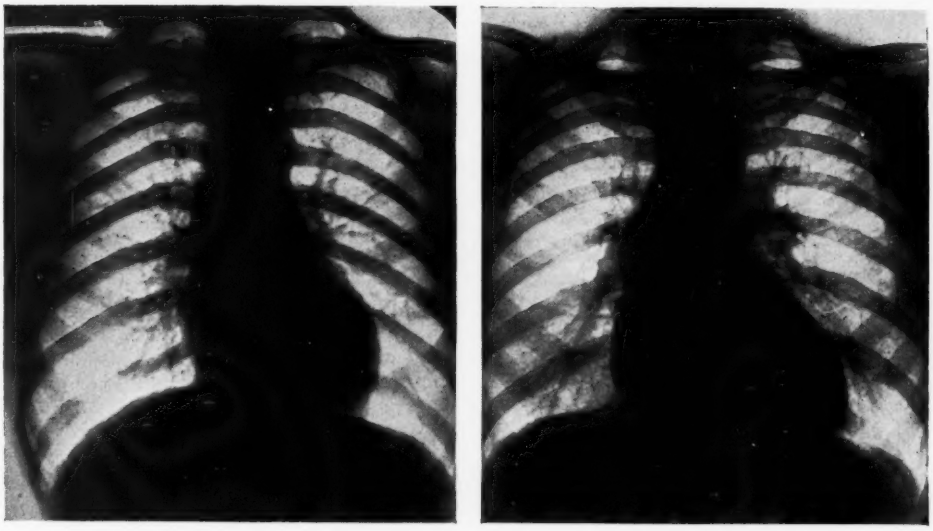

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FIG. 6.—The heart in congenital aortic stenosis in adults, showing the same prominence of the aorta, and that the heart may or may not be enlarged. (A) From a man, aged 39, showing no cardiac enlargement (c.t.r. 45%), though he had much anginal pain. Case 38. (B) With rather more prominence of the first part of the aorta, from a man, aged 49, with early heart failure (c.t.r. 53%). Case 37.

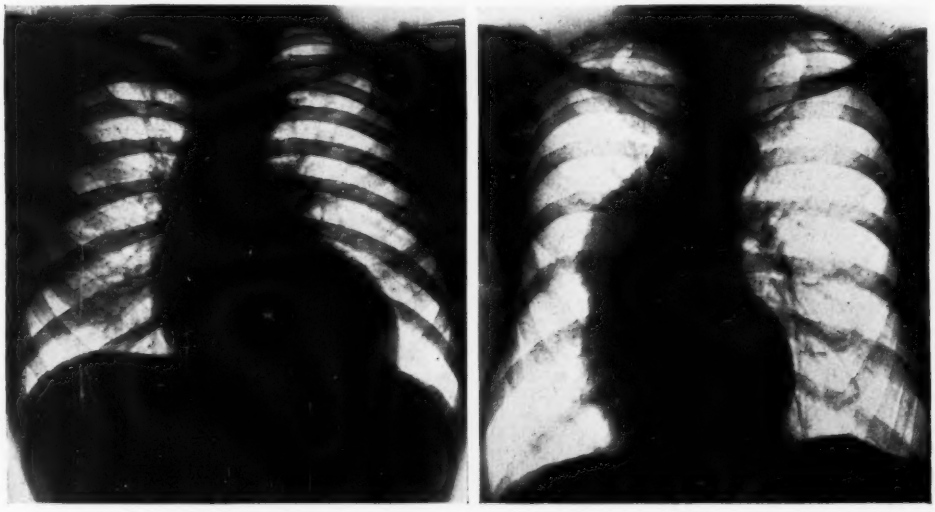

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FIG. 7.—(A) One of the largest hearts (c.t.r. 56%) seen in congenital aortic stenosis, looking more like the usual picture of left ventricular enlargement secondary to aortic incompetence. From a man, aged 28, who had developed aortic incompetence. Case 29. (B) The most extreme example of dilatation of the first part of the aorta, still without any enlargement of the heart (c.t.r. 45%) from a man, aged 50. Case 25.

it was detected and we think that few patients are without some calcification after 30 and very few after 40 years of age. Gibbs (1935), in 26 necropsies of cases of aortic stenosis found calcification common in the rheumatic and almost invariable in the atherosclerotic ones, sometimes as early as the fourth decade and commonly in the fifth decade.

Electrocardiograms. Left ventricular strain, namely, S–T segment depression and T wave flattening or inversion over the left ventricle, was present in 22 of these cardiograms, occurring in patients as young as two years (Case 3) or, if he is excluded, six years (Case 9). Its development is illustrated in Fig. 2, 8, and 9 and the following history is given as an example.

Case 30. A boy of 12, without any significant symptoms, was referred because of a murmur that had been found when he had pneumonia two years before. There was a rough systolic murmur and thrill, maximum in the pulmonary area. The cardiogram was normal (Fig. 8A). The diagnosis made by one of us was congenital pulmonary stenosis.

When 28, he was working as a draughtsman and again attended hospital. There had been moderate dyspnœa and sub-sternal tightness on vigorous exertion since he was 16, but walking had never been troublesome. He was hypersthenic. The systolic thrill was now felt best to the right of the midline and the murmur was heard over the whole præcordium, and louder to the right. On fluoroscopy the ascending aorta was unduly prominent and the left ventricle slightly enlarged. Calcification of the aortic valves was not on this occasion seen, but was evident a year later. The cardiogram was now that of left heart strain with a transverse electrical axis (Fig. 8B).

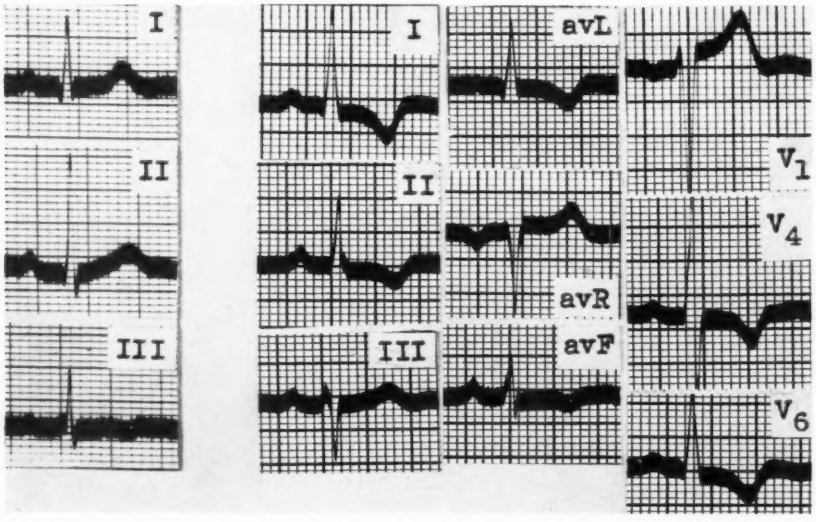

FIG. 8.—Electrocardiograms showing the development of left ventricular preponderance and strain. (A) When aged 12, with a normal cardiogram. (B) When aged 28, with left ventricular strain. Case 30.

The combination of a vertical electrical axis with left heart strain was noted in nine instances (Fig. 10): there is no suggestion that in these the axis becomes transverse later. Kiloh (1950) drew attention to the vertical electrical axis in two of his cases with left ventricular strain (20 per cent of those studied cardiographically) but did not find left ventricular preponderance as often as we have. That the electrical axis should remain vertical when left heart strain is present might be attributed to the muscular hypertrophy being concentric, yet in seven of the nine patients a diastolic murmur was present and the aortic incompetence, even though trivial, may well have

TABLE

SOME CLINICAL FINDINGS IN OUR 40 PATIENTS WITH CONGENITAL AORTIC STENOSIS

Case	Age and sex	Age heart queried	Rh.F. and age of onset	Effort dyspnœa	Effort angina	Cardiac impulse	Systolic thrill	Early D.M.	A.2	B.P.	Left ventricle	Aorta and valves: Widened	Aorta and valves: Hyperdynamic	Aorta and valves: Calcified valves	Electrical axis	L.V.S. and age noted	Type
1	8 M	Birth	—	Slight	—	N	+	—	—	105/75	—	—	—	—	Vertical	—	V
2	25 F	6/12	—	Always slight	Moderate	N	++	+	—	120/90	—	—	+	—	Vertical	24	V
3	4 F	10/12	—	—	—	LV	+++	++	(—)	110/70	++++	+	+	—	Transverse	2	V
4	3 M	11/12	—	—	—	N	++	—	—	100/80	+(+)	—	+	—	Vertical	—	V
5	38 M	12/12	±7–10	Moderate 36	*Slight 36	LV	++	+	—	125/90	+(+)	+	—	++	Vertical	35	V
6	12 M	12/12	—	Slight	—	N	+	—	N	80/65	+(+)	(+)	—	—	Vertical	—	S
7	37 F	15/12	—	Moderate always	*Moderate	LV	+	—	N	115/95	+	++	—	+	Transverse	37	V
8	3 F	20/12	—	—	—	N	+	—	N	—	+ and RV+	—	—	—	Vertical	—	S
9	6 M	24/12	—	—	—	LV	++	+	(—)	95/70	+	—	—	—	Vertical	6	V
10	9 M	24/12	—	—	—	N	++	—	N	105/65	—	—	—	—	Transverse	9	S
11	9 M	30/12	—	Slight	—	LV	++	—	+	100/85	+	+	++	—	Vertical	—	S
12	19 M	3	±5	—	—	LV	+	—	N	130/85	++	(+)	+	—	Transverse	16	S
13	6 M	3	—	—	—	N	+	+	N	110/70	(+)	—	—	—	Transverse	6	V
14	9 M	3	—	—	—	N	+	—	N	90/70	+	(+)	—	—	Vertical	—	S
15	8 M	3	—	—	—	N	+	+	N	95/70	+	+	—	—	Transverse	—	V
16	5 M	3	—	Slight	—	N	++	—	N	95/65	+	—	—	—	Vertical	—	S
17	7 M	4	—	Slight	—	N	++	—	(—)	105/70	+	—	—	—	Vertical	7	V
18	34 F	4	+7	Moderate 30	—	LV	+++	—	(—)	105/80	++	++	—	—	Transverse	32	V
19	38 F	5	—	Moderate 14	*—	LV	++	—	—	100/80	(+)	+	—	—	Transverse	25	V
20	24 F	5	—	—	—	N	++	+	+	100/80	(+)	(+)	(+)	—	Transverse	24	V
21	9 F	6	—	Slight	—	LV	++	—	(—)	100/85	+	(+)	(+)	—	Vertical	—	V
22	8 F	7	—	Slight	—	LV	+++	±	(—)	105/90	++	(+)	—	—	Vertical	7	V
23	7 M	7	—	—	*—	LV	+	—	(—)	105/65	+	(+)	+	—	Vertical	7	V
24	18 M	8	±14	Slight 16	Slight	N	++	+	+	155/120–85	+	+	+	—	Transverse	—	V
25	50 M	8	—	Slight	—	LV	+++	++	(—)	120/80	+	+++	++	+++	Transverse	39	V
26	23 M	9	—	Slight	Slight 22	LV	++	+	(—)	100/60	++	—	+	++	Vertical	22	V
27	35 M	9	—	Moderate 34	*—	LV	++++	—	N	130/90	++	+	—	(+)	Transverse	L BBBI	V
28	29 M	9	+9	Slight 17	*Slight 17	LV	++	+	N	135/115	(+)	—	—	+	Vertical	29	V
29	29 M	10	—	—	—	LV	++	+	+	135/75	++	+	+	+	Vertical	28	V
30	32 M	10	—	Slight 16 Worse 30	Slight 16	N	++	—	(—)	110/90	+	++	—	+	Transverse	28	V
31	12 M	10	—	—	—	N	++	+	—	105/65	—	+	—	—	Transverse	—	V
32	48 M	10	—	Severe 46	*Severe 46	LV	++	—	(—)	105/85	++	+	+	+	Transverse	40	V†
33	13 M	12	—	Slight	—	N	++	+	N	110/80	++	(+)	+	—	Vertical	—	V
34	15 M	13	—	Slight	Slight 13	N	+	++	N	105/85	+	+	+	—	Transverse	—	V
35	17 M	15	—	—	—	N	++	—	N	120/85	+	+	+	—	Transverse	—	S
36	25 M	18	—	Slight	—	LV	++	++	(—)	145/110	+++	++	+	—	Transverse	25	V**
37	49 M	19	—	Slight 27 Severe 48	—	LV	++	—	+	110/90	+++	+	(+)	—	Transverse	49	V†
38	40 M	37	—	Severe 38	*Moderate 38	LV	+	++	(—)	120/65	+	+	+	++	Vertical	R BBBI 39	V**
39	42 M	39	—	Moderate 40	Slight	LV	+	(+)	N	115/95	++	+	—	+	Transverse	—	V
40	42 M	42	—	—	—	N	++	—	N	140/90	(+)	+	+	—	Transverse	—	S

N = Normal. — = absent. (—) = diminished. * = Effort syncope. A.2. = Aortic second sound. L.V.S. = Left ventricular strain.
** = Subactue bacterial endocarditis. † = Confirmed post mortem. V = Valvular. S = Subvalvular.

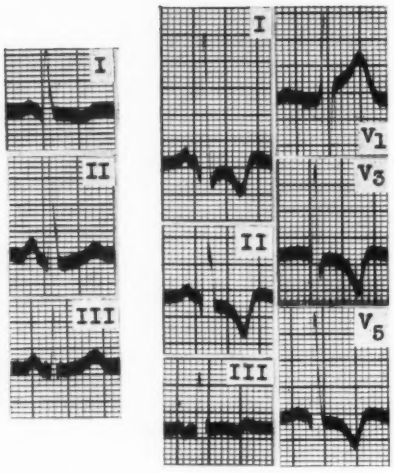

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FIG. 9.—Electrocardiograms showing increasing left ventricular strain. (A) When aged 39, with slight inversion of TI. (B) When aged 50, with deep inversion of S–TI and other signs of left ventricular strain. Case 25.

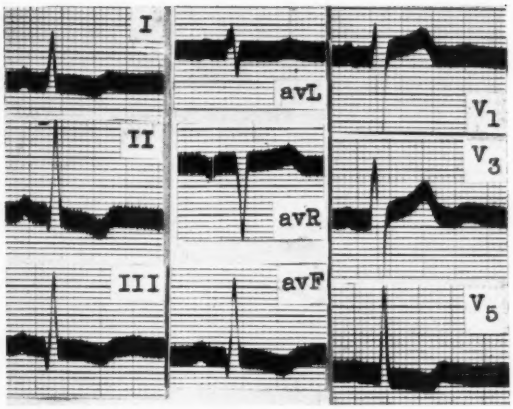

FIG. 10.—Electrocardiogram, showing the common combination of a vertical electrical axis with left ventricular strain. Case 29.

played some part. Conversely, in thirteen patients with a transverse electrical axis and left heart strain there was a clinically pure stenosis in eight.

A low T wave in aVF or aVL may be the first evidence of developing ventricular strain, either to be confirmed forthwith in V7 (Case 26) or to appear later in præcordial records. Left heart strain was occasionally seen without obvious fluoroscopic ventricular enlargement (Cases 2 and 10). Alternatively moderate left ventricular enlargement was present without cardiographic heart strain (Cases 33 and 39). Left bundle branch block occurred in Case 27, aged 35, and right bundle branch block in Case 38, aged 40.

THE INCIDENCE OF VALVULAR AND SUBVALVULAR AORTIC STENOSIS

Congenital aortic stenosis has been regarded as rare (White, 1951) though Wood (1950) thought that subaortic stenosis was less rare and formed two per cent of his congenital cases. Congenital aortic stenosis is certainly not very rare, for among 460 acyanotic cases seen in 1947–51 there were 32 with aortic stenosis (7 per cent or nearly 3 per cent of all the congenital cases), and we think most of these had valvular stenosis.

In the 1000 cases analysed by Maud Abbott (1936) there were 18 with subaortic and 11 with valvular stenosis compared with 105 with coarctation of the aorta. There are relatively few post-mortem reports of subvalvular stenosis, and Kiloh (1950) was able to find less than 40 cases in all. Necropsies of congenital valvular stenosis are equally uncommon, but we think this is because of its good prognosis and the difficulty of recognizing the congenital ætiology when the patient dies late in life. In our view congenital aortic stenosis is relatively common, and this is supported by the papers of Gallavardin (1936), Young (1944), and Kiloh (1950).

Brown (1950) thinks it difficult to differentiate valvular and subvalvular stenosis, but that those with valvular stenosis are more likely to have the typical pulse of aortic stenosis, a diminished or absent aortic second sound, and an aortic diastolic murmur, though this has been found with a a bicuspid valve and subaortic stenosis: they are also more likely to have calcification of the valves

though subvalvular calcification has been reported. In both the enlargement of the left ventricle may be small and there may be some dilatation of the aorta and the electrocardiogram may be normal or may show left axis deviation. In both the symptoms may be slight and the lesion may be found at routine examination, but both are prone to the risk of bacterial endocarditis. His own experience of 43 cases suggested that the pulse is normal in about one-third of them. Wood (1950) thinks that patients with subaortic stenosis differ in having a clear second sound, a normal pulse, little enlargement of the left ventricle, and a good prognosis.

In our cases the allocation to the valvular as opposed to the subvalvular type has depended on the presence of visibly calcified valves, and to a lesser extent of an aortic diastolic murmur, and of an impaired second sound. On such a basis 31 cases were considered valvular and 9 subvalvular. The oldest patient, with the exception of one aged 42 (Case 40), who was thought to have subvalvular stenosis was 19 years of age (Case 12).

The quality of the pulse and its pressure merely indicate the severity of the lesion and may not help in differentiation unless we can assume that valvular stenosis is generally more severe than subvalvular: if so, the subvalvular stenoses are further reduced. The post-stenotic aortic dilatation is probably without value in differentiation.

Prognosis

In Abbott's series (1936) the average period of survival with aortic valvular stenosis was 3·75 and the maximum was 24 years, while with subaortic stenosis the figures were 22·6 and 58 years. Brown (1950) also thinks the prognosis much better in cases with subaortic stenosis, and Wood (1950) says that most patients with aortic valvular stenosis die young, but that there is a good prognosis in those with subaortic stenosis.

In our own experience the prognosis in valvular stenosis is good in children and few patients have severe symptoms till they reach adult or even middle age, when the outlook becomes more serious. Gallavardin (1936) emphasized the good prognosis of valvular stenosis, stating that few of his patients under 25 had any symptoms and that even between 25 and 50 only about half had severe symptoms. The absence of necropsies in the series of Gallavardin and Kiloh and ourselves, except for two patients of about 40 who died after aortic valvotomy, seems to confirm this view. We have, however, found two specimens in the Guy's Hospital Museum where children have died, one very suddenly and one with heart failure rather suddenly, as a result of congenital aortic stenosis. Dr. Keith Simpson informs us that among the 30,000 coroners' necropsies that he has performed he remembers about six with congenital aortic valvular stenosis in addition to these two reported in the next section, but can not remember any with subaortic stenosis: there have, of course, been many older patients with severe aortic stenosis, but they have been regarded as rheumatic or atherosclerotic, though he has been much impressed by the large proportion without mitral stenosis.

We must, therefore, modify the view that the prognosis is always good by realizing that occasionally the stenosis is so severe that death may follow early.

Cases with Necropsy

We shall describe shortly the clinical and post-mortem findings in these two patients and in the two of our series who died after aortic valvotomy. The fusion of the valves and their irregularity in the two younger are more in keeping with a congenital than an inflammatory origin. In the older two the degree of secondary change and of calcification makes a decision more difficult, but one of them appeared to have a bicuspid valve and we think the balance of evidence is that here, too, the original lesion was congenital.

Case 32. This man knew that he had a murmur since childhood; he had never had rheumatic fever. He had no symptoms until 1944, when at the age of 40, he had severe dyspnœa and sternal pain after running in the Home Guard. There was a rough systolic murmur and thrill over the sternum: the heart was of normal size and the blood pressure 120/80. There was left axis deviation and TI was slightly inverted. He was thought to have slight pulmonary stenosis. Two years later he saw Dr. Bramwell and Dr. Towers

who found the same signs and diagnosed aortic stenosis: his pain in the chest, which was now more frequent and more easily provoked, was accepted as anginal.

He was first seen by us in 1952, aged 48, because during the previous year walking even 25 yards provoked sternal pain and dyspnœa, though afterwards he could walk up to a quarter of a mile slowly. There was a rough systolic murmur and thrill maximal in the mid-line at the base; no diastolic murmur was heard. The blood pressure was now 105/85. The maximum transverse diameter of the heart increased to 15·0 from 13·7 cm. in 1947 (c.t.r. 54 from 49%). On screening, the left ventricle was enlarged, but there was nothing to suggest mitral stenosis: the first part of the aorta was somewhat dilated and pulsated freely, and calcification of the aortic valves was easily seen. His cardiogram showed left ventricular preponderance with deeper inversion of TI.

The diagnosis made was pure aortic stenosis, probably congenital, and an operation was advised in view of his severe disability and deterioration. He was admitted to hospital within two months, but had developed congestive heart failure. At cardiac catheterization the pressure in the brachial artery was wider than the clinical estimate, i.e. 112/60 mm. and in the pulmonary trunk 70/35; the pressure in the right atrium, 27/14, was also raised. The cardiac output was 3·4 litres a minute and hardly changed with exercise. His failure improved but did not disappear with treatment and there was still some pericardial effusion.

At operation the pressure was 216/36 in the left ventricle against 112/76 in the aorta. Mr. Brock was able to increase the aortic opening and his condition was satisfactory for some hours, but signs of left ventricular failure increased, and he died that night.

Necropsy. The left ventricle was much hypertrophied. The pulmonary and tricuspid valves were normal. The mitral orifice was normal and the valve was normal except for heavy calcification spreading from the aortic valve over the base of the aortic cusp. The coronary orifices and arteries were normal, and the aorta showed no general atheroma: there were nutmeg changes in the liver, which was slightly cirrhotic.

The appearance of the aortic valve is shown in Fig. 11: there was a very small irregular central opening about 4 by 1 mm., which had been split at operation to the periphery on one side, but not on the other, making a total length of 12 mm. There was severe, craggy calcification of the cusps, and the only part that might have been fairly mobile was to either side of the split. It was not easy to be certain about the commissures, but the valve seemed bicuspid with only two sinuses, though about the middle of the slightly larger sinus there might have been the remnant of another commissure.

FIG. 11.—The aortic valve viewed from above, from a man, aged 48, who died after aortic valvotomy. Gross craggy calcification of a valve that was probably bicuspid. At operation there was only a small central opening which was successfully split to the posterior border, but not anteriorly because of the gross calcification. Case 32.

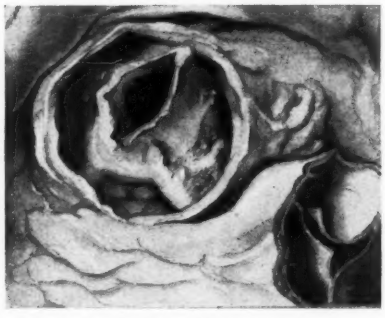

FIG. 12.—The aortic valve from above, from a man, aged 50, who died after aortic valvotomy. The valve was probably tricuspid, but is fibrous and calcified. The original opening was thought to be small and central, but here it has been opened to its maximum capacity after being split at operation. Case 37.

Case 37. This man had no history of rheumatic fever but was always rather breathless playing games and was told there was a murmur at a routine examination when he was 19 and again 8 years later when he had pneumonia; the blood pressure was then 110/80. After this he was a little breathless, but worked as a

male nurse until 1950, when he was 48. The lesion was then recognized as pure aortic stenosis, and though he was given easier work he continued to lose ground.

He was first seen by us when he was 49 years old. The distance he could walk had fallen from two miles to half a mile, and stairs had become difficult. There was a rough systolic murmur and thrill in the aortic area, and a slow rising anacrotic pulse with a blood pressure of about 102/85. No diastolic murmur was heard. The heart was a little enlarged, and on screening this was shown to be due to the left ventricle; the first part of the aorta was prominent and pulsatile. The cardiogram showed left ventricular preponderance with some inversion of T in leads I and V5.

During the next six months he found he could not manage the light work he had done before, and became anxious for aortic valvotomy. The heart was larger, c.t.r. 58 (17·5/30), but decreased after treatment to 53 per cent (16/30 cm.). The liver was enlarged and tender and there was a small effusion at the right base which cleared up with rest, digoxin, and a low salt diet. A direct reading of the pressure in the brachial artery was 96/60, and in the pulmonary trunk 32/14.

At operation on 23/10/52 the pressure was 172/8 mm. Hg in the left ventricle and about 70/50 mm. in the aorta. Mr. Brock was reasonably satisfied with the increase in the size of the valve opening, but ventricular fibrillation started during the operation, and though it was stopped with the defibrillator, the blood pressure remained below 70 and the pulse rate rose from 110 to 140. He developed signs of pulmonary œdema, and died the next morning.

Necropsy. The left ventricle was much hypertrophied with some subendocardial fibrosis, and there seemed to be some hypertrophy of the right ventricle as well. The aorta was normal except that it seemed constricted where it was joined by the commissures, the sinuses of Valsalva being deeper than usual, and it was a good deal dilated beyond this.

There was severe stenosis of the aortic valve from fusion of the three cusps with much thickening and calcification (Fig. 12). The orifice was oval and, after valvotomy, measured about 13 by 5 mm. between the posterior and left anterior cusps. The heart showed no other abnormalities.

Guy's Hospital Museum Specimen 2309. This girl, aged 15, had been under medical care for some 10 years since her congenital heart disease had been recognized. She complained of tiredness while out one day and went to bed. Two days later a doctor was called and found some congestion of the lungs and œdema of the legs: a high-pitched systolic murmur was heard in the aortic area and up the neck. The next morning she was found dead in bed.

Necropsy. There were general signs of congestive heart failure, but no other abnormality was found outside the heart. The valves were normal, except for the aortic. It was difficult to say how many cusps there had been as the valve appeared like a continuous thickened diaphragm projecting as a cone into the aorta, but it seemed more likely to have been bicuspid. The orifice measured 6 by 3 mm. and was made rigid by great thickening and rolling of its edges. The cusps were thickened in most parts, though there was one translucent area in what appeared to be the largest cusp, the furthest away from the pulmonary opening (Fig. 13). There was no obvious calcification. The aorta was hypoplastic, and smaller than the pulmonary trunk, about 13 mm. against 18 mm. There was gross concentric hypertrophy of the left ventricle and also some of the right ventricle presumably because a failing left ventricle had transmitted the increased pressure to the right side of the heart: if so, it is surprising that there was not a longer history of increasing dyspnœa, but the history available was not detailed. The heart weighed 765 g.—an enormous heart for a girl of this age.

Guy's Hospital Museum Specimen 2308. This boy, aged 11, collapsed and died while playing with other boys at home. He was of normal build, but had been somewhat short of breath and had been under medical supervision at school for congenital heart disease. There were said to be high-pitched systolic and diastolic murmurs in the aortic area; he was not greatly disabled and was able to attend school normally.

Necropsy. No abnormality was found outside the heart. The mitral valve was normal and so was the rest of the heart except the aortic valve and the left ventricle. The heart weighed 340 g. There was concentric hypertrophy of the left ventricle and some scarring of its muscle due to the edge of the valve turning over the orifice of the left coronary artery. The aortic cusps were difficult to distinguish and the valve was a conical shape and consisted of thickened connective tissue covered by smooth endothelium, rising to a small orifice towards the upper left-hand margin of the valve (Fig. 14). This opening was no more than 3 by 2 mm., and it seemed difficult to think that it could ever have been central. Looked at from below, the valve was even more conical, with the opening at the top, but asymmetrical. The greater part of the valve cusps were hard and nodular, but did not appear to be calcified. The aorta was small, 10 mm. in diameter.

FIG. 13.—The aortic valve from above, from a girl of 15 who developed congestive failure and died suddenly a few days later. The cusps are grossly abnormal and fused; there were probably two only, but it is difficult to be sure of this. The small opening is eccentric and somewhat posterior and to the left. The pulmonary trunk was larger than the aorta. Case No. 2309.

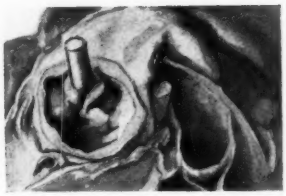

FIG. 14.—The aortic valve from above, from a boy, aged 11, who died suddenly. The cusps were completely fused so that the number cannot be recognized and the valve was very irregular and funnel-shaped. The opening could hardly be seen, so a probe has been passed through it. It was eccentric, being rather posterior and to the left. Case No. 2308.

DISCUSSION OF ÆTIOLOGY

Monckeberg (1904) assigned aortic stenosis to acute endocarditis or slowly developing valvular sclerosis. This dual ætiology, infective and degenerative, attracted equal support until the publication of Karsner and Koletsky's (1947) monograph in which evidence of rheumatic infection was found in no less than 196 of 200 patients with aortic stenosis: there were two examples of congenital bicuspid aortic valves with marked stenosis, showing the congenital ridge, neither of which revealed rheumatism histologically. Previously Sophian (1945) had remarked that histologically rheumatism was so frequent that its presence did not prove that the ætiology was rheumatic. There must always be great difficulty in evaluating the previous disease process represented in scarred and calcareous aortic valves; evidence of rheumatic infection elsewhere in the heart may not be decisive and must be assessed in the knowledge of the natural history of the disease and of the case: otherwise the discipline of histology becomes tyrannical rather than salutary. Karsner and Koletsky (1947) suggest that only with rare exceptions is calcific disease of the aortic valve not due to rheumatism. It is peculiar that in their series no less than 26 per cent of the hearts were essentially normal in weight, and we think that many of these were much more likely to be congenital.

The natural history of rheumatic fever is that of recurrent infection culminating in failure of the myocardium. The aortic valves may be affected alone, but then pure aortic stenosis is relatively rare (Campbell and Shackle, 1933). Most often there is gradual progression from aortic incompetence to some degree of aortic stenosis, which may remain unimportant or become severe. With congenital aortic stenosis, however, there is no impairment in the constitution, repeated cardiac failure does not occur, the incompetence comes after the stenosis, if at all, and the stenosis is often gross at an age when with rheumatism this would be improbable. This is not to state that a pure stenosis cannot be rheumatic, but under the age of thirty it is more likely to be congenital.

Marvin and Sullivan (1935) discussing the ætiology of aortic stenosis said that they referred to it as atherosclerotic because it seemed that the signs and symptoms were not due to the original lesion, but rather to the calcareous changes that occurred only after the passage of many years.

Gallavardin (1909, 1921, and 1936) first emphasized the frequency of a type of aortic stenosis that was not rheumatic " qui se caractérise par sa tendance particulière á réaliser le retrécissement aortique pur et que cette cause doit-être recherchée en dehors des atteintes rhumatismales franches ou frustes." In 1936 he described 50 cases that closely resemble those we have described: half of them were under 25 and half between 25 and 50, cases older than this being excluded. All were

thought to have aortic stenosis, but less than half seem to have had a striking thrill. Over one-third had an aortic diastolic murmur, but it was never loud. The pulse was never water-hammer; it was sometimes normal or small and often showed the features of aortic stenosis. Nearly four-fifths of the patients were men. A few had angina or syncope on effort. He gave good reasons for thinking the patients were not rheumatic, but did not accept them as congenital. He thought that there might have been an endocarditis of unknown origin in fœtal life, and drew an analogy with cases of pulmonary valvular stenosis, but this is now widely accepted as a true congenital lesion and not due to inflammatory changes before birth: we think that this is also true of the cases of aortic stenosis.

Young (1944), reporting 12 cases that were found in soldiers between 19 and 30 years of age who were free from symptoms, thought that these were subaortic stenosis, presumably only because he thought the prognosis better in this group. Kiloh (1950) describes his findings in 26 cases of pure aortic stenosis, those over 50 being excluded. He agreed with Gallavardin's view that they were not rheumatic, but thought there was no final answer to the ætiology without necropsy evidence. In many of his cases, as in Gallavardin's, the signs were found at routine examination. He found, generally, slight enlargement of the left ventricle on radioscopy, and more frequently, dilatation of the first part of the aorta, which he thought particularly important for diagnosis in these young patients without hypertension Calcification of the aortic valves was seen in half his cases

From consideration of the present material we think the ætiology of aortic valvular stenosis may be more accurately assessed from the history, progress, and physical signs than from autopsy material, and that by analogy the diagnosis of congenital heart disease may be made initially in adult life. Ideally, the lesion should have been recognized prior to the age of four, and this applied to nearly half the patients of the present series. But the valvular lesion is progressive and symptoms are late in appearance, so that early diagnosis is generally made only at a routine medical examination, when there may be confusion as to the nature of the congenital lesion.

A Note on Arterial Dilatation Beyond a Constriction

The nature of the arterial dilatation beyond an aortic or pulmonary valvular stenosis has aroused much interest. Chevers (1842) referred to the thinning and dilatation of the first part of the aorta with valvular stenosis and attributed it to " the long continuance of a degree of stagnation in the contents of the tube," or, alternatively, to the fixed valves remaining rigid in diastole, thereby causing the whole weight of the blood to impinge upon the sides of the aorta. This dilatation distal to a constriction is not easy to understand, but Professor G. Stead has given us a physical explanation based on Bernouilli's principle that, when a liquid flows through a tube that is not uniform in diameter, pressure on the walls is greatest when the velocity is least. If a liquid is flowing through a tube the velocity (v) must be increased (to V) when it is flowing through the narrow part. A mass (m) of liquid will therefore gain momentum when it enters the constriction and lose it again when it emerges. The loss of momentum ($mV–mv$) after passing the constriction must be brought about by an opposing (or braking) force acting in the opposite direction to the flow, and thus the pressure must be higher on the far side of the constriction. For the same reason it is higher on the proximal side, but this does not imply that it must be the same on both sides because, owing to the viscosity of the blood, the difficulty of forcing it through the constriction will lead to a lower pressure on the distal side. The very low pressure often observed beyond pulmonary valvular stenosis makes this explanation more difficult for pulmonary than for aortic stenosis. In the instance in question this higher pressure and turbulence beyond the constriction will lead to a dilatation of the aorta, while on the proximal side the pressure is taken by the hypertrophied ventricular muscle.

This conception of a pressure higher beyond than within a constriction is not easy to understand in that blood appears to be flowing from a level of low pressure to a level of high pressure, but these principles of hydrodynamics provide some explanation, and post-stenotic turbulence may be another factor. Perhaps the way a river widens and its banks fall away *below* a constriction, such as a weir, is an analogy that makes it easier to understand.

Summary and Conclusions

Congenital aortic stenosis, especially valvular stenosis, is not uncommon. It may pass unrecognized for many years or even till the stenosis is made more severe by the addition of fibrosis and calcification. We think that the aortic stenosis of many patients presenting in middle life is often congenital in origin.

We have described 40 cases of congenital aortic stenosis in nearly half of which the murmur was heard before they were four years old, and have discussed the implications of the history and clinical findings. We have described the necropsy findings in two of these, and in two other children.

The main points in the diagnosis are the recognition of heart disease early in life without a history of acute rheumatism; the systolic murmur and thrill of aortic stenosis without evidence of mitral stenosis; a heart that is not much enlarged, often with the minor enlargement of the left ventricle persisting with little change over the years, even when there are cardiographic signs of left ventricular strain; and some prominence of the first part of the aorta, best seen in the left anterior oblique position. This dilatation and pulsation of the first part of the aorta are helpful in the diagnosis, with the clinical background. The combination of a vertical electrical axis with left ventricular preponderance and often strain, in the absence of mitral stenosis, is suggestive of congenital aortic stenosis.

In the more severe cases, but not in the others, there will be a small, slow-rising pulse and a low pulse pressure. Later, there may be aortic incompetence, but it is generally slight. The aortic second sound is diminished in about half the cases. Calcification of the aortic valves was seen once before the age of 20, was common after 30, and was the usual finding after 40 years of age.

Generally, dyspnœa is slight or even absent, and there are few symptoms until 25 or 30 years of age or even later. Except in the most severe cases, the prognosis is good, at least until middle age. Serious symptoms are often absent until calcification and sclerosis make the stenosis more severe.

The evidence we have brought forward for this picture of congenital aortic stenosis is mainly clinical. We think that the pathological basis for the ætiological diagnosis of aortic stenosis needs reconsideration in the light of these views.

We are grateful to Mr. R. C. Brock for the notes about the findings at operation in Cases 32 and 37, and to Dr. H. E. Holling for the pressure readings in these patients. We should like to thank Miss M. Waldron for the drawings of the aortic valves, and Mr. C. Engle for the photography.

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PAROXYSMAL TACHYCARDIA IN PREGNANCY

BY

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There are conflicting views regarding the incidence of paroxysmal tachycardia in pregnancy. Jensen (1938) concluded from a review of the literature that there had been only 19 cases reported up to 1938 in which the diagnosis was beyond reasonable doubt, and he thought that the condition was rare during pregnancy. On the other hand, Campbell (1947) was of the opinion that paroxysmal tachycardia is far more common in pregnancy than is generally recognized. The purpose of this paper is to review briefly the relevant papers and to analyse ten personally observed cases.

Campbell and Elliott (1939) discussed the influence of pregnancy in 7 of a series of 100 patients with paroxysmal tachycardia. Jensen *et al.*[1] (1940) observed three cases of paroxysmal tachycardia in a series of 108 pregnant patients with organic heart disease. Hamilton and Thomson (1941) stated that they were able to make a satisfactory diagnosis of paroxysmal tachycardia during pregnancy in 13 out of 781 patients with rheumatic heart disease. Browning and Clark (1941) reported two cases of paroxysmal tachycardia occurring during pregnancy. Single cases were reported by Weyler and Dustin (1942), Lian *et al.* (1948), and by Abbas and Guild (1951). Vander Veer and Kuo (1950) studied 409 pregnant patients with heart disease and found paroxysmal tachycardia in six. They considered this to be a high incidence and suggested that pregnancy may predispose to paroxysmal tachycardia.

Personal Observations

We were able to make a satisfactory diagnosis of paroxysmal tachycardia in pregnancy in ten cases. There were several more patients who complained of attacks of palpitation, with sudden onset and offset, and who very probably were suffering from true paroxysmal tachycardia, but in the absence of electrocardiographic or clinical confirmation were not included in this series. The ten cases analysed in the present paper were observed during a ten-year period (1942–52). The total number of patients with heart disease seen and followed up in one or more pregnancies during this ten-year period was 380. The total number of pregnant patients delivered in the department of obstetrics during the same period was 10,746.

Six patients had rheumatic heart disease, and in four no lesions were detected.

There were four primiparæ and six multiparæ. Two of the multiparæ had attacks in more than one pregnancy. One patient had attacks in three successive pregnancies but never between pregnancies.

Paroxysms of tachycardia occurred during pregnancy in eight patients. In six of these the attacks appeared in late pregnancy, and in two they started early and became more frequent in the latter months of pregnancy. One patient who had frequent attacks during pregnancy developed an attack during labour. Attacks occurred during the puerperium in six patients. Two of these had attacks in the puerperium only and none during pregnancy or labour.

In eight patients we were able to obtain cardiograms during paroxysms of tachycardia. In all eight the tachycardia was of the supraventricular type (Fig. 1).

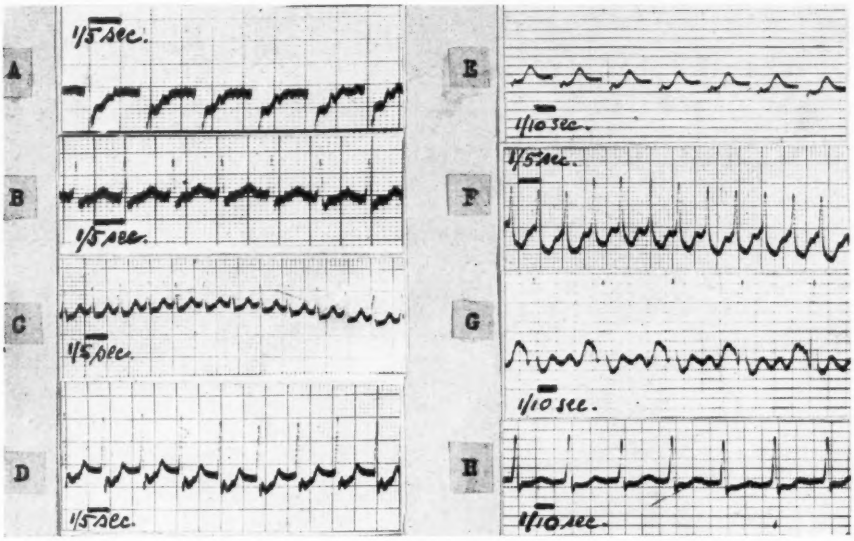

FIG. 1.—Lead II in eight cases (A-H) of paroxysmal supraventricular tachycardia complicating pregnancy.

DISCUSSION

The observations of Anderson (1932, 1933) in two patients with paroxysmal tachycardia are of interest: one who had frequent attacks since the age of six years was free from attacks during her pregnancy and had only one attack seven days after delivery; the other had attacks only during pregnancies and never between pregnancies. Similarly, Campbell and Elliott (1939) said that in two of their patients the attacks became less frequent during pregnancy, while five patients were unfavourably influenced by pregnancy. In 19 cases details are available as to the appearance of the first paroxysm: eleven patients had attacks prior to pregnancy while in eight the attacks first appeared in pregnancy or in the puerperium. In our series, in one case the history was inadequate because of the mental condition of the patient; in the remaining nine the first attack occurred during pregnancy or in the puerperium. Six out of these nine patients had paroxysms only in relation to pregnancy while three had occasional attacks during a follow-up period of 32 months, 28 months, and 3 months, respectively, following delivery. Accordingly, these observations favour the idea that pregnancy tends to increase susceptibility to paroxysmal tachycardia. Four of the patients in the present series were receiving digitalis before the onset of paroxysmal tachycardia, but it is very unlikely that digitalis caused the attacks in any of these four.

In nearly all cases, including the present group, the tachycardia was of the supraventricular type. As far as we are aware the only published case of ventricular tachycardia confirmed by electrocardiogram occurring during pregnancy is that of McMillan and Bellett (1931–32); in this case frequent paroxysms occurred in the latter part of pregnancy and the patient was delivered by cæsarian section during such a paroxysm. Mackenzie (1921) mentions a patient who was studied with the polygraph and who was thought to have paroxysmal ventricular tachycardia during pregnancy. The electrocardiogram in one of our cases shows a 2 : 1 A-V block (Fig. 1G). This

tracing may be regarded by some as an example of auricular flutter, but the various clinical and cardiographic features observed in this patient conform to the definition of paroxysmal tachycardia as postulated by Evans (1944). Evans (1944) and also Campbell (1945) have drawn attention to the occurrence of A-V block in paroxysmal tachycardia. It is possible that the tracings of some of our other patients also showed 2 : 1 A-V block, but adequate chest leads were not available in each instance for the study of this special point. Two of our patients also had auricular fibrillation, and this interchangeability of rhythm has also been observed (Evans, 1944).

According to Carr and Hamilton (1933) paroxysmal tachycardia does not make pregnancy dangerous provided there is no structural heart disease; on the other hand, it can be a dangerous complication if mitral stenosis is present. They observed heart failure in several patients, with a fatal outcome in one, among their seven cases of heart disease complicated by paroxysmal tachycardia. Campbell (1947*a*) and Gilchrist and Haig (1950) have also stated that the prognosis entirely depends on the underlying disease. Our observations show that paroxysmal tachycardia in the presence of organic heart disease can precipitate heart failure: it did so on four occasions in three patients. The attacks that were associated with heart failure lasted 12 hours, 6 hours, 72 hours, and 24 hours, respectively. In three patients with rheumatic heart disease the paroxysms were at no time associated with heart failure. Here, the longest attack lasted 1 hour, 1 hour, and 1½ hours, respectively. Similarly, no heart failure developed in four patients without structural heart disease. In these four patients the longest attack lasted 17 hours, 1 hour, 46 hours, and ½ hour, respectively. From these observations it would appear that a long paroxysm of tachycardia in the presence of organic heart disease must be considered as a serious complication and every effort should be made to restore normal rhythm as soon as possible. It is also our impression that paroxysmal tachycardia is of more serious consequence during pregnancy than in the puerperium, but the numbers are not large enough to enable us to draw definite conclusions in this respect.

Hamilton and Thomson (1941) used ipecacuanha with success in five patients with paroxysmal tachycardia in the puerperium and in one patient during pregnancy. They observed no ill effects and suggested that the drug can be safely used during pregnancy and the puerperium in the absence of congestive heart failure or recent operation when violent vomiting is to be avoided. They also had good results with digitalis; occasionally, they used quinidine. Browning and Clark (1941) and Abbas and Guild (1951) also used quinidine. These authors believe that there is no adequate evidence to support the general belief that quinidine or associated alkaloids precipitate labour. According to Sollmann (1942) quinine or quinidine has no effect on the uterus unless labour pains have started. We used digitalis in six patients—oral medication in four, and intravenous followed by oral medication in two. The impression gained was that in four patients digitalis was responsible for the termination of the attack, while in two patients spontaneous termination was a strong probability. One patient was given procaine amide, after termination of the attack, 2½ grams daily for 4 weeks, in an attempt to prevent recurrences. However, she had a recurrence during procaine amide medication on the eighth day following mitral valvotomy. It is possible that the dose was inadequate. Four patients received no drugs; in one of these the attack stopped after violent vomiting. We have not used quinidine during pregnancy so far, but procaine amide which has a quinidine-like action on the heart was used for one patient without any harmful effect on the course of pregnancy. Pressure on the carotid sinus failed to restore normal rhythm in six patients.

SUMMARY

Ten cases of paroxysmal tachycardia complicating pregnancy are reported. Paroxysms of tachycardia occurred during pregnancy in eight patients, during labour in one, and during the puerperium in six. The present observations favour the idea that pregnancy tends to increase susceptibility to paroxysmal tachycardia.

Paroxysmal tachycardia in the absence of structural heart disease does not seriously interfere with the normal course of pregnancy. On the other hand, if associated with structural heart

disease it can precipitate heart failure. This statement is based on observations on rheumatic heart disease; no cases of paroxysmal tachycardia associated with cardiac disease other than rheumatic heart disease were seen during pregnancy.

We are grateful to Dr. W. G. A. Swan for his criticism and help. We also wish to thank Dr. R. Orton for permission to include a case under his care.

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CARDIOVASCULAR DISEASE IN A RANDOM SAMPLE OF ELDERLY PEOPLE

BY

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The observations that follow give some indication of the prevalence of the commoner cardiovascular diseases, including cerebrovascular accidents and the disability resulting therefrom, in a random sample of 476 elderly people living at home in Sheffield. They are based on full clinical examinations which were carried out in the subjects' homes.

The importance of cardiovascular disease in the elderly needs no emphasis. It accounted for 42 per cent of all deaths of men over pensionable age (65+) and the same percentage of all deaths of women over pensionable age (60+) in England and Wales in 1949 (Int. List Nos. 90–103). If deaths from intracranial lesions of vascular origin (Int. List No. 83) are added, the figures become 54 and 58 per cent.

Of the 476 subjects, 192 were men and 284 women. Eighty per cent of the men and 47 per cent of the women were over 70 years of age.

Derivation of Sample

In 1948, a social survey had been carried out by the Council of Social Service on a 1 : 30 sample of all Sheffield people of pensionable age, (Greenlees and Adams, 1950). The sample had been selected by a random procedure from the food office register. The group of elderly people used in the medical survey was derived from this sample and included all those living alone or living alone with spouse who could be traced and agreed to be examined. Those living alone or alone with spouse were chosen to facilitate a dietary survey which was carried out at the same time. Of 736 possible subjects, 260 were not available when the medical survey came to be done. Sixty-four had died. Thirty-six were no longer living alone or alone with spouse, 18 had left Sheffield or could not be traced, and in 142 cases, consent for the examination was withheld. As two years had elapsed between the two surveys, the youngest women in the medical survey were 62 and youngest men 67. The sample included all social classes and we believe was reasonably representative of elderly people living independently at home. There was, however, a slightly higher proportion of women and of representatives of the higher income groups amongst the refusals. Ninety-four per cent of the medical examinations were carried out by one physician (H.D.).

Previous Surveys

Sheldon (1948) appears to have been the only other investigator to have reported on a medical survey of old people in their homes. He interviewed 477 old people but did not carry out an examination of the cardiovascular system or measure the blood pressure. Gavey (1949) described the cardiovascular conditions found in 360 elderly people attending hospital for ophthalmic and other conditions including cardiac conditions. Neither of these surveys is strictly comparable with ours, the former, because similar investigations were not carried out, and the latter because the subjects were largely selected on account of sickness. Where possible, however, in the absence of more comparable material, we have compared the findings of these authors with our own.

In a health survey which includes those who are not ill as well as those who are, it is sometimes difficult to know how to classify people in whom morbid conditions are found that are not causing symptoms. This problem is particularly prominent when considering cardiovascular disease in

the elderly, as few people over 65 do not show some evidence of degeneration of the heart or blood vessels. Arteriosclerosis and hypertension, often with no symptoms, are so common that they have been excluded from consideration here except for the few cases of heart failure in which hypertension appeared to be an important cause. The data on the blood pressures have been published elsewhere (Droller *et. al.*, 1952).

In trying to assess the importance of cardiovascular disease in this group, it appeared to be preferable in the first place to concentrate on those who were to some extent disabled by these conditions. What follows, therefore, is primarily concerned with the 87 subjects (18 per cent of the whole sample) whose activity was limited by cardiovascular disease. Some indication has also been given, where possible, of the numbers who had signs of these conditions with few or no symptoms and whose activity was apparently unaffected.

Analysis of Function and Effect of Age

The functional analysis was based mainly on the subject's own assessment of his activity. According to his description, he was placed in one of four categories.

1. Outside unlimited activity
2. Outside limited activity
3. Confined to the house
4. Confined to bed.

Of the 87 whose activity was limited, only 2 were bedridden; both were women suffering from hemiplegia after a cerebrovascular accident. Four men and 16 women were confined to the house, and the remainder were able to undertake a limited amount of out of door activity such as pottering about the yard or calling on neighbours.

There were too few cases in our series to assess the effect of age on the incidence of the separate conditions, but when both sexes and all cardiovascular conditions were combined, there was an increase in the incidence of disablement with age from 6·8 per cent at age 60–64 to 30·8 per cent age 75 and over. The overall incidence was slightly higher in the women, 20 per cent, than in the men, 16 per cent.

Diagnosis and Degree of Disablement by Heart Disease

The diagnosis of those whose activity was judged to be limited by cardiovascular disease and the degrees of limitation are shown in the Table.

Angina of effort. Angina of effort was the commonest condition found. Thirty-one subjects (6·5 per cent of the whole sample) suffered from angina to an extent sufficient to limit activity but a further 99 (20·5 per cent) complained of the symptom to a lesser degree. The condition was equally frequent in men and women. It was remarkable how many of those with angina refused to allow it seriously to interfere with their activities. For example, 13·5 per cent of the men with angina were still in whole-time employment. This figure may be compared with the 21 per cent of all the 192 men still in employment.

Pulmonary heart failure. Thirty-two (7%) of the total sample were disabled by chronic bronchitis, emphysema, and bronchospasm, and of these, four men and five women (2 per cent of the whole sample) had developed chronic cor pulmonale.

Chronic bronchitis and hypertension were not infrequently associated and it was difficult in some cases to decide in cases of early heart failure in which both were present, whether the cardiac failure was of pulmonary or hypertensive origin.

The records were examined to see whether the incidence of hypertension was abnormally high in those with chronic bronchitis. Altogether 189 of the 476 subjects suffered from some degree of chronic bronchitis, usually accompanied by emphysema and occasional wheezing. Of the 189 with bronchitis, 40 per cent had systolic blood pressures of 180 or more while of the 262 without

bronchitis, 48 per cent had blood pressures of 180 or more. This difference was shown by the X^2 test to be not statistically significant. Neither was bronchitis any commoner in those with diastolic pressures of 100 mm./Hg or more, than in those with pressures under this figure. There does not therefore appear to be any significant association between chronic bronchitis and high blood pressure in the elderly. The two conditions are both so common that they inevitably often occur together.

Hypertension and heart failure. Nineteen per cent of the men and 29 per cent of the women had a systolic blood pressure of 190 mm./Hg or more and 28 per cent of men and 48 per cent of women had a diastolic pressure of 100 mm./Hg or more. In other words, on these criteria, approximately one-third of the subjects had hypertension. A good many of these also had various combinations of the following symptoms and signs: angina of effort, dyspnœa on slight exertion, chronic cough and wheezing, emphysema, and nocturnal dyspnœa. So much was this so, that we found it difficult to diagnose " hypertensive heart disease " as an entity with confidence. In nearly all the cases with high blood pressure as defined above in which there were signs of heart failure, other conditions such as coronary artery disease or chronic bronchitis with emphysema and bronchospasm were present which could have been responsible for the heart failure. Finally, and with some doubt, we allotted 9 cases (3 men and 6 women) to the group " hypertensive heart failure."

The examinations tended to confirm the view that hypertension in those over 65 is usually benign. In a special study of the blood pressure in this group of elderly people (op. cit.) we showed that high sphygmomanometer readings showed no statistical correlation with angina pectoris, enlargement of the heart judged radiologically, or the subject's well-being and activity.

Cerebrovascular accidents. In many cases, it is impossible to nurse the elderly patient who has

INCIDENCE OF CARDIOVASCULAR DISEASE CAUSING LIMITATION OF ACTIVITY IN 476 ELDERLY PEOPLE

	192 Men			284 Women			All 476	Percentage of whole sample
	Bed-ridden	House fast	Limited outdoor	Bed-ridden	House fast	Limited outdoor	Some limitation	
Angina of effort ..		1	11		3	16	31	6·5
Pulmonary heart failure ..		1	3		3	2	9	2·0
" Hypertensive heart failure " ..			3			6	9	2·0
Cerebro-vascular accident.. ..		1	1	2	5		9	2·0
Rheumatic heart disease			1		1	4	6	1·3
Degenerative aortic disease ..		1	1		1	3	6	1·3
Peripheral vascular disease			3				3	0·6
Syphilitic aortic disease			1			1	2	0·4
Miscellaneous ..			3		3	6	12	2·5
TOTAL ..		4	27	2	16	38	87	18·0

had a cerebrovascular accident at home, and so he or she is admitted to hospital. For this reason, it is not a very common finding in old people at home. Where an elderly person who has had a stroke is kept at home, either voluntarily or because of difficulty in securing admission to hospital, the burden on the relatives may be very heavy.

Altogether, there were 7 women and 2 men (2 per cent of the sample) whose activity was limited by cerebrovascular accidents. Sheldon found 4 per cent in his series, but he included patients who had recovered from a stroke.

Rheumatic mitral disease. One man and 5 women were to some extent disabled by rheumatic heart disease. That is, an incidence of 1·3 per cent. Several of these cases had other possible causes of disablement, including angina, in addition to the rheumatic lesion.

Angina is described as a rare symptom in mitral stenosis. White (1944) states that it is " almost always due to an incidental complication of coronary heart disease." The proportion of subjects with mitral stenosis who also had angina was similar to the proportion who had angina in the whole sample. It would seem likely that the angina in these subjects was due to concurrent coronary artery disease, rather than to the rheumatic heart disease.

Degenerative aortic valve disease. Two men and 4 women had degenerative aortic valve disease causing reduced activity and other symptoms. In addition, there were 2 men and 1 woman with this condition who had no limitation of activity. The total incidence therefore was 2 per cent. Gavey found an incidence of 1·7 per cent.

Of the 9 cases, 4 had both systolic and diastolic aortic murmurs, 4 had aortic systolic murmurs only and 1 had an aortic diastolic murmur only. The subjects with regurgitation were more disabled than those in whom stenosis was the prominent feature. Two of the 5 with regurgitation were confined to the house, but none of the 4 with stenosis.

Peripheral vascular system. There were no cases of senile peripheral gangrene. Intermittent claudication was the most disabling variety of peripheral vascular disease that was encountered. There were 20 men and 9 women who had this symptom in some degree, but only in 3, all men, was it bad enough to limit activity.

Disabling intermittent claudication in the elderly would appear to be practically confined to men and its incidence in them to be about 1·5 per cent. Sheldon and Gavey both found a similar incidence.

Syphilitic aortic disease. There were only two examples of syphilitic aortic disease discoverd in our series, a woman of 65 and a man of 68. In both, the blood W.R. was positive and in both their activity was limited by the disease, though in the case of the man, the limitation was not severe.

Syphilitic aortic disease is not common now. Even in the elderly, the incidence appears to be less than 0·5 per cent, and because of recent advances in treatment, it should eventually become rare. Gavey found no cases in his series.

Congenital heart disease. No cases of congenital heart disease were discovered. Gavey found one case out of 360 patients. It appears to be very rare for persons with congenital heart disease to survive the age of 60.

Auricular fibrillation and congestive cardiac failure. Auricular fibrillation was diagnosed on the basis of the clinical examination alone as no electrocardiographic examinations were made. The incidence, therefore, is possibly an underestimate. Three men (1·5%) and 12 women (4%) had this irregularity and the underlying cardiac conditions were varied. It was usually a sign of serious cardiac disease. Eleven of the 15 subjects whose hearts were fibrillating were limited in their activities and 6 had developed congestive cardiac failure. It may be noted that of the whole sample, only 3 men and 11 women (3%) were found to have congestive cardiac failure.

Heart Disease Secondary to Disease in Other Organs

Renal heart failure. No cases of heart disease that could be attributed to renal disease were found. This excludes those subjects with various degrees of albuminuria with or without hypertension in which renal atherosclerosis was probably present.

Thyrotoxic heart disease. There were 5 subjects, all women, who had thyroid enlargements and evidence of heart disease. In only one did it appear that the heart condition was due to toxic changes in the thyroid.

Myxœdema and heart disease. There were 3 cases of myxœdema (1%), all women. All had hypertension.

Osteitis deformans and cardiovascular disease. The findings in the small group of proved cases of Paget's disease in this series, 7 men and 2 women, suggested that osteitis deformans predisposes to, or aggravates existing cardiovascular disease (Edholm, Howarth, and McMichael, 1945). Only those cases with at least two of three criteria of Paget's disease—clinical evidence, radiological evidence, and serum alkaline phosphatase of 35 units or above—were included. Of the 7 men, all had marked clinical arteriosclerosis, 5 had low systolic and diastolic blood pressures, 3 had early congestive cardiac failure, and 2 degenerative aortic incompetence; 4 of the 5 whose chests were radiographed had enlarged hearts. These findings were all much commoner in the cases of Paget's disease than they were in the whole sample. There were too few cases amongst the women to justify comment.

Cardiovascular disease of mixed or indeterminate ætiology. In a good many of the cases in this series, more than one pathological process was contributing to the disability. In some, pulmonary disease was co-existent with cardiac disease, in others, more than one type of cardiovascular disease was present, for example, coronary artery disease and mitral stenosis. Where it was found to be impossible to classify a case under a single cardiac heading, it was classed as mixed or indeterminate.

In old age, the heart may fail at last, not from one but from several causes. It may then be very difficult, as experienced general practitioners know, to make a more precise diagnosis than "heart failure." As this term is unacceptable for the purposes of registration, such cases are often diagnosed as myocarditis or myocardial degeneration and go to make up the huge total of deaths ascribed to these causes in England and Wales; 85,134 in 1949, or 49 per cent of all circulatory deaths.

Summary and Conclusions

A random sample of 476 people over pensionable age living at home, alone or alone with their husband or wife, were examined clinically. The incidence of the various cardiovascular disorders is given and the amount of disability caused by them is described. In 18 per cent of the sample, there was some limitation of activity due to this group of diseases.

Angina of effort was the commonest disorder found, followed by pulmonary heart disease, hypertensive heart failure, and cerebrovascular accidents in equal numbers. Then came rheumatic heart disease, degenerative aortic disease, peripheral vascular disease, and syphilitic aortitis. A miscellaneous group included some cases of heart disease secondary to other diseases such as osteitis deformans or thyrotoxicosis and a group of cases in which there appeared to be more than one cause of heart failure, for example, coronary artery disease and mitral stenosis. A surprisingly large number of the subjects who had evidence of cardiovascular disease were not apparently limited in their activity.

The general picture of cardiovascular disease in this group of elderly people which emerged was, as would be expected, one in which conditions resulting from arterial degeneration predominated. Many had evidence of a gradual cutting off of the cardiac circulation with the consequent cardiac pain and limitation of activity. In a smaller number, interruption of the circulation had occurred in more distal parts such as the brain causing paresis and mental changes, or the legs causing intermittent claudication. Syphilitic heart disease now appears to be rare in the elderly, but rheumatic heart disease is not very uncommon if the incidence of 1·3 per cent found in this series is representative. Chronic cor pulmonale accounted for 2 per cent of the cases and with the more effective treatment of acute exacerbations of chronic respiratory disease in the elderly which is now possible, this variety of heart failure may well become more common in the future. There was no significant association between chronic bronchitis and hypertension.

The most striking finding was not the number who were disabled but the much greater number who, in spite of having multiple signs of cardiovascular disease, were living full and active lives. In the whole sample of 476, there were only 2 who were bedridden and 20 who were confined to their homes because of cardiovascular disease. It is of course true that a good many elderly people with serious cardiovascular disease are admitted to hospital and that the small number of bedridden old people in this series does not give a true indication of the total number of serious cases of cardiovascular disease in the elderly population. However, a rough calculation based on the number of hospital beds in Sheffield normally occupied by the elderly, and on the assumption that half are occupied by patients with cardiovascular disease, indicates that only about 8 additional bedridden cases would have to be added to this sample to make it representative.

We wish to thank Professor W. Hobson and Miss C. Roseman for their helpful suggestions in the preparation of this paper.

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COMPARISON OF OPERATION AND CLINICAL FINDINGS IN MITRAL STENOSIS AND INCOMPETENCE

BY

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Experience gained with surgical treatment of the diseased mitral valve has increased our knowledge of its function. At operation the surgeon can observe the character and degree of the pulsation of the atrium, and on opening the atrium he can judge with his finger the size of the valve orifice, the state of the valve cusps, and whether or not a regurgitant stream can be felt. Direct measurements of the pressure within the heart chambers can be made. It is therefore possible to compare the state of the valve at operation with the findings in the examinations before operation.

In most cases of mitral stenosis selected for valvotomy it is found that the valve orifice is not more than 1·0×0·5 cm. in size. The valve cusps retain considerable flexibility as is shown by the manner in which they bulge into the atrium during ventricular systole, and, even if a regurgitant jet is felt before the commissures are divided, clinical improvement follows adequate separation of the cusps (Baker *et al.*, 1952). In other cases with a similar sized orifice the cusps are more rigid from fibrosis and calcification, and valvotomy is difficult to achieve because of this. Even if the cusps are separated with a knife, their relative immobility prevents the valve opening, and clinical improvement does not follow.

We have had experience of a further group, also with rigid margins, but with a valve orifice appreciably larger and a palpable regurgitant stream. These cases appeared to be clearly unsuitable for valvotomy, not only because of the rigidity of the valve cusps but also because, as the stenosis was less, proportionately less improvement could be expected to follow its relief. In the cases with the largest orifices, the surgeon considered there was no stenosis and that rigid or shrunken cusps were failing to close the valve aperture during ventricular systole.

From these observations it follows that in the selection of cases for valvotomy it is important to be able to exclude those with wide orifices and rigid cusps. We have examined the records of such patients to see whether they presented any characteristic features. For the reports of the findings at operation we are indebted to Mr. R. C. Brock. Dr. Maurice Campbell and Dr. Charles Baker were the physicians in charge of these patients.

MATERIAL

We have analysed the clinical, radiological, and electrocardiographic features and the results of cardiac catheterization in the 96 cases in which at the time of analysis the valve had been explored at operation. In 61 no regurgitation had been felt, and all these were found to have an orifice of less than 1·0×0·5 cm.: these we have called cases of pure mitral stenosis. The remainder had a palpable regurgitant stream; 26 had small orifices of similar size to the cases of pure mitral stenosis; 9 had rigid valve orifices greater in size than 1·25×0·75 cm. The group of 26 intermediate cases have been put on one side in order to throw into contrast any distinguishing features between the group with pure mitral stenosis and the group with comparatively wide, rigid valve orifices, and palpable regurgitation.

* Work undertaken on behalf of the Medical Research Council.

TABLE I
THE SIZE OF THE MITRAL ORIFICE IN MITRAL INCOMPETENCE

Case No.	Size of orifice (in cm.)	Case No.	Size of orifice (in cm.)
G 76	1·25×0·75	G 73	3·0×1·5
G 57	1·25×0·75	G 83	4·0×1·5
G 77	1·75×1·0	G aa	4·0×2·5
G 53	2·0 ×1·0	G 116	3·0×1·5
G 36	2·5 ×10		

Of the 9 cases with wide, rigid orifices four had been diagnosed as having predominant stenosis. In Cases G 57, G 73, G 116, and G 77 considerable mitral regurgitation had been suspected and it was intended, if this was confirmed, to insert a pericardial flap to lessen the degree of regurgitation. The ninth (Case G aa, reported elsewhere by Venner, 1953) had been diagnosed as mitral incompetence together with constrictive pericarditis, and the state of the valve was determined at operation for pericardectomy.

METHODS

Pressure records were made with an electrical condenser manometer (Peterson, 1949). When recording pulmonary capillary pressure the catheter was advanced along the pulmonary artery until it reached a branch small enough to be occluded by the cather tip. The pressure then recorded was believed to be that in the pulmonary capillaries, or more probably the pulmonary veins (Lagerlöf and Werkö, 1949; Hellems, Dexter *et al.*, 1949).

Fig. 1 shows a pulmonary capillary pulse record obtained in pure mitral stenosis; on it is superimposed the pulmonary artery pulse taken from the same patient. In the pulmonary capillary pulse two pressure waves to each cardiac cycle can be distinguished; they have been termed the A

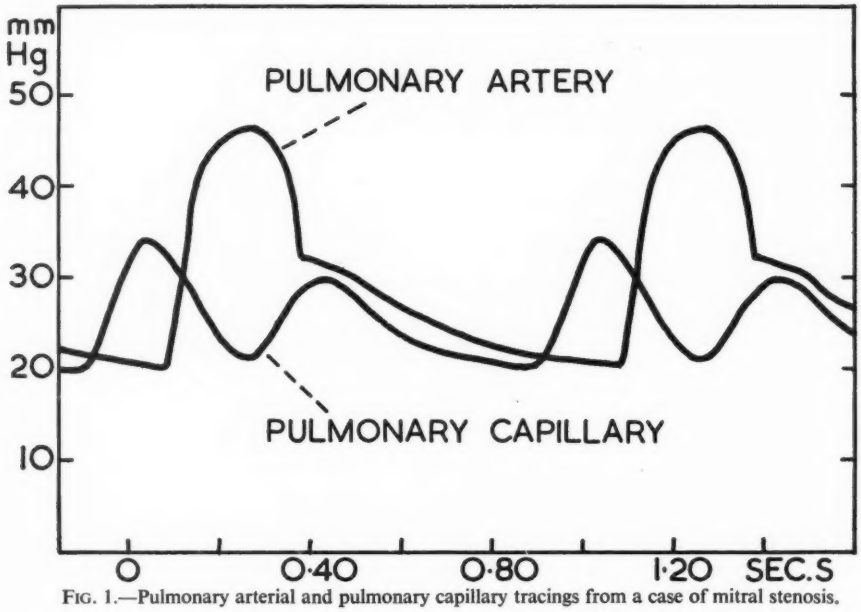

FIG. 1.—Pulmonary arterial and pulmonary capillary tracings from a case of mitral stenosis.

and the V wave. The A wave is so called because it appears to be due to atrial systole and is not seen when there is auricular fibrillation.

In only about half our cases have we been able to obtain a satisfactory pulmonary capillary record. In those with large hearts the catheter may make a wide loop in passing through the heart, and insufficient length is left for the tip to be advanced into a small vessel. In some cases a damped pulmonary artery pulse is recorded, even though the catheter tip seems to be wedged in a small vessel. When the characteristic A and V waves shown in Fig. 1 are present the record can be accepted as a pulmonary capillary pressure pulse. In cases of auricular fibrillation where the A wave is absent we have adopted the following criteria. There should be the feeling, particularly on withdrawal, that the catheter is wedged in the vessel in which it lies; aspiration of blood from the catheter should yield either arterialized blood or no sample at all; and the main pulse wave of the pulmonary capillary should be delayed compared with the pulse wave of the pulmonary artery. Often, however, the record is obscured by artefact and is unsuitable for analysis.

In most cases the records were taken in quick succession through the double lumen catheter using a single manometer. From such records the timing of the peak of the V wave relative to the dicrotic notch of the pulmonary artery pulse was determined by measurement from the simultaneous electrocardiogram, choosing sections with an equal heart rate. Measurements were made from at least five beats, and the mean of these recorded. More recently, simultaneous pulmonary capillary and pulmonary artery records have been made with a double lumen catheter, using two manometers.

Left atrial and ventricular tracings were recorded at operation by puncture with a 21-gauge needle connected to the manometer by a metre of hardened plastic tubing of 1·4 mm. internal bore. Until two manometers became available we recorded the two tracings in quick succession and later superimposed them by measurement from the simultaneous electrocardiogram.

Findings

History and Symptoms. There were no significant differences of age and sex incidence, or duration of severity and type of symptoms between the group of 9 cases with wider mitral orifices and those with pure mitral stenosis. Six of the nine gave a history of rheumatic fever, two of frequent hæmoptyses, four of attacks of paroxysmal dyspnœa, and six of congestive heart failure. Eight of the nine cases had auricular fibrillation.

The Apex Impulse. The normal apex impulse has a short thrusting character. With cardiac hypertrophy this quality usually becomes more obvious, giving a lifting impulse. When the left ventricle is predominantly and markedly involved in the hypertrophy the apex impulse has a sustained heaving quality. In contrast, in mitral stenosis the apex has a short tapping quality. A note had been made on the character of the apical impulse in 41 of the 61 cases of pure mitral stenosis. In two of these it was described as normal Five cases were said to have a lifting impulse at the apex, but they had significant aortic valve disease in addition to their mitral stenosis. In the others, the impulse was described as tapping. Of the 9 cases with wider orifices, no record was available in one: the impulse described as tapping in two only while in six it was described as lifting, and in only two of these could this be ascribed to aortic valve disease.

Auscultation. With the exception of the case of constrictive pericarditis all the patients had a mid-diastolic murmur. In one at least (G 116) this was of very short duration.

All systolic murmurs appeared to start with the first sound and occupied the major part or all of systole, and there were no examples of short or late systolic murmurs. They were graded according to their loudness by Levine's (1945) method (Table II). Of the 61 cases subsequently found to have no palpable regurgitation, 13 had an apical systolic murmur. All those with wide mitral orifices had an apical systolic murmur, though in one it was only of Grade II intensity. The quality of the murmur did not serve to distinguish the two groups; in both, all Grade IV murmurs were described as harsh and the Grade II and III murmurs were described as either harsh or blowing.

TABLE II

APICAL SYSTOLIC MURMUR IN MITRAL VALVE DISEASE

State and function of mitral valve at operation	Intensity of murmurs (Levine's classification)		
	Grade IV or more	Grade III	Grade II or less
61 cases of mitral stenosis ..	1 (with thrill)	6	6
8 cases with regurgitation ..	4 (2 with thrill)	3	1

In three of the cases with wide mitral orifices the first heart sound showed the abrupt quality associated with mitral stenosis, but the opening snap was absent. An opening snap was heard in Case G 73 with the third largest mitral orifice. Triple rhythm, due to the addition of a third heart sound, was heard in three cases, but not in any of those with pure mitral stenosis.

Size of Heart. The mean cardiothoracic ratio of the 61 cases with pure mitral stenosis was 56 (range 46 to 71), whereas in the 9 with wider mitral orifices it was 64 (range 53 to 76).

Left Ventricular Hypertrophy. In the 9 patients unsuitable for valvotomy electrocardiographic records showed no evidence of ventricular hypertrophy in 4; right ventricular hypertrophy in 3; and in the 2 others, who had aortic valve disease also, one showed left ventricular hypertrophy and the other both left and right ventricular hypertrophy. Cardiographic evidence of left ventricular hypertrophy was not therefore a diagnostic feature; nor was the absence of right ventricular hypertrophy, for it was absent also in one-fifth of those with pure mitral stenosis without aortic valve disease.

At screening, enlargement of the left ventricle was remarked in only 4 of the 9 unsuitable for valvotomy, and in 3 of these a clinical diagnosis of aortic valve disease had been made.

Systolic Expansion of the Left Atrium. At fluoroscopy the 9 cases with wide mitral orifices showed enlargement of the left atrium, but not more than most of those with small orifices. In only two, G aa and G 116 (Table I), was systolic expansion of the left atrium seen whereas " expansile pulsation " was recorded in 5 of the cases of pure mitral stenosis. In Case G aa pulsation was seen in both anterior-posterior and right oblique views.

Findings at Catheterization. Table III shows the cardiac indices, pulmonary artery and pulmonary capillary pressures in those with wide rigid orifices. The mean of the values obtained does not differ significantly from that of the cases of pure mitral stenosis with a similar degree of disability.

TABLE III

	Pulmonary artery pressure (mm. Hg.)	Pulmonary capillary pressure (mm. Hg)	Cardiac index (l./sq.m./min.)
Pure mitral stenosis ..	52 (41)	25 (27)	2·0 (40)
Mitral regurgitation ..	52 (9)	26 (5)	2·0 (8)

The figures in parentheses refer to the number of patients.

Pulmonary Capillary Tracings. Lagerlof and Werko (1949) state that the V wave is taller and broader when mitral incompetence is present. Soulié states that pulmonary capillary curves provide written and objective proof of the presence of mitral regurgitation, for he finds that when he has diagnosed this condition, whether auricular fibrillation is present or not, the peak of the V wave occurs 0·04 to 0·08 seconds before the end of the period of pulmonary ejection, whereas in mitral

stenosis the summit of the V wave occurs immediately after this period (Soulié *et. al.*, 1951). The dicrotic notch of the pulmonary artery tracing is taken as the end of the ejection period. In our cases the summit of the V wave occurred after the dicrotic notch of the pulmonary artery tracing in those with pure mitral stenosis and those with wide orifices alike. Neither did the height of the V wave serve to distinguish the two groups. The results obtained from our measurements of the V wave in 12 cases with pure mitral stenosis and 5 with wide mitral orifices are summarized in Table IV.

TABLE IV

HEIGHT AND TIMING OF V WAVE IN THE PULMONARY CAPILLARY TRACING IN CASES OF MITRAL VALVE DISEASE

Diagnosis (confirmed at operation)	Height of V wave (mm. Hg)		Time of peak of V wave after dicrotic notch of pulmonary artery tracing (seconds)	
	Mean	Range	Mean	Range
12 cases with no palpable regurgitation	8	3–30	0·07	0·01 to 0·12
5 cases with palpable regurgitation (Cases G aa, G 53, G 57, G 77, G 116)*	16	9–32	0·04	0·02 to 0·06

* All cases with auricular fibrillation.

Left Atrial Pressure Tracings. In no case could systolic expansion of the left atrium be seen by those present at operation, or felt by the surgeon; not even in cases G aa and G 166, in whom it had been seen at fluoroscopy. We were able to record pressure pulses from the left atrium and ventricle in most of the patients and in all the nine with wide rigid orifices. Fig. 2 shows representative tracings from three with pure mitral stenosis and auricular fibrillation, for comparison with those obtained from three others with a wide mitral orifice. In Fig. 3 are given the maximum pressures recorded in pure mitral stenosis and in the 9 with wide mitral orifices. It will be seen that the rise in pressure in the left atrium during ventricular systole was no greater in the group with wide mitral orifices, and presumably marked mitral regurgitation, than in the group with pure mitral stenosis. Wynn *et al.* (1952) obtained similar results.

DISCUSSION

Where there was a wide rigid orifice the apical systolic murmur was loud, and the surgeon did not encounter such an orifice in a patient in whom no systolic murmur has been heard. However, a loud murmur, and even a thrill, is not a certain indication that the valve is unsuitable for valvotomy, for one case had a Grade IV murmur and a thrill and yet proved to have a small orifice with supple valves and no regurgitation. In an unselected series of cases of mitral stenosis the proportion with a loud systolic murmur, yet suitable for valvotomy, would be higher, for in the past such a murmur has been a point against selection for valvotomy. We have not found that any particular character of the murmur is associated with those unsuitable for valvotomy. The occurrence of a third heart sound would seem to be a point against advising valvotomy, but this sign is recognized with difficulty when there is a mid-diastolic murmur, and such a murmur is necessarily present in a case being considered for mitral valvotomy.

Absence of a tapping quality of the apex impulse would appear to be an indication that the valve is unsuitable for valvotomy. According to Logan and Turner (1952) the slapping quality of the first heart sound that is associated with mitral stenosis is faint or absent in cases of predominant incompetence. Though no note was made on this in most of our cases, it is a point that we have recognized as being of value.

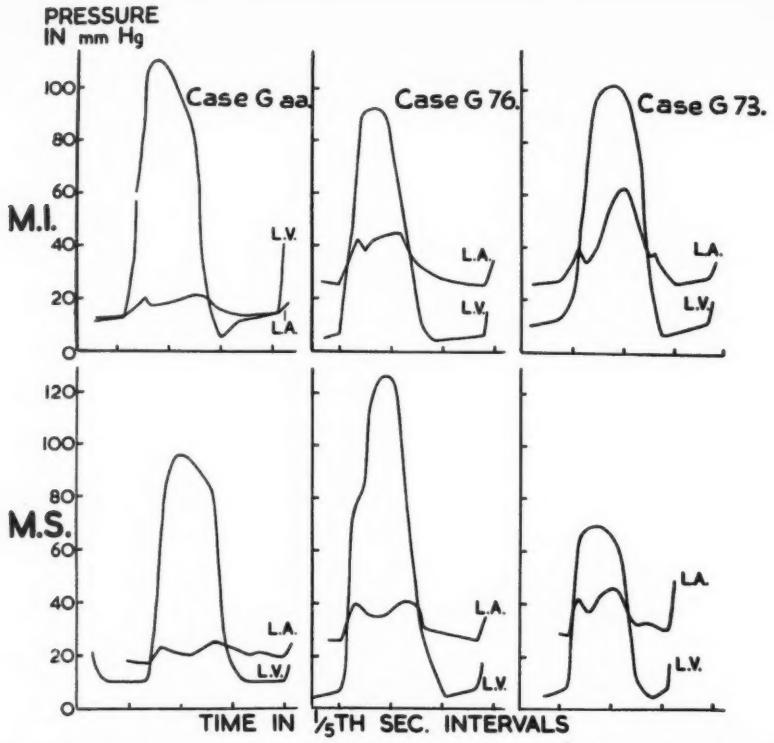

FIG. 2.—Left ventricular and left atrial pulse tracings from three cases with palpable regurgitation and orifices greater than 1·25×0·75 cm. (M.I.), and three cases of mitral stenosis with no palpable regurgitation (M.S.). All cases had auricular fibrillation.

Expansile pulsation of the atrium on fluoroscopic examination has been found in only two of the cases with a rigidly open orifice, and enlargement of the left ventricle in only four (and in three of these the ventricular enlargement might have been due to coexisting aortic valve disease). A retrograde pressure wave from the contracting left ventricle was not detectable in the pulmonary capillary tracings, nor even in those from the left atrium. Thus the signs that are believed to result from the regurgitation of a considerable volume of blood were not in practice found to be a feature of this group.

Our results show that investigation by radiological methods and cardiac catheterization failed to distinguish the cases with wide, rigid valve orifices, but some help was afforded by palpation and auscultation. The recognition of these before operation is difficult and the physician must expect to have his assessment occasionally upset at operation. If he rejects all those with a systolic murmur this will be less likely to happen, but some will be unnecessarily rejected. If the condition of the mitral valve is in doubt in a patient for whom surgical treatment is otherwise indicated, it is justifiable to perform a surgical exploration of the valve.

Mitral regurgitation. When the knowledge of the effects of rheumatic heart disease on the function of the mitral valves was based on the appearance of the valve post mortem, it was presumed that considerable quantities of blood regurgitated through the diseased mitral valve with

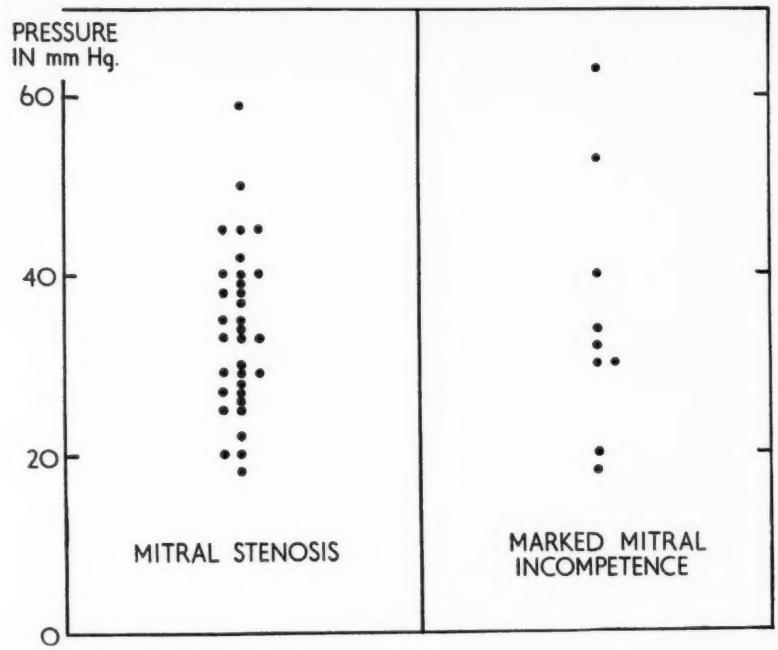

FIG. 3.—Maximum pressure in the left atrium in cases of mitral stenosis (left) and the cases of marked mitral incompetence (right).

a wide, rigid orifice. Gorlin (1952) has put forward an ingenious method of calculating the volume of regurgitation and finds that the volume is such that the rigid mitral orifice is obstructed during ventricular systole: the method, however, involves a number of assumptions and no method of checking the results exists. Our findings indicate that the volume of blood regurgitated is smaller than had been thought. Though the surgeon can feel a regurgitant stream in cases with a wide, rigid orifice, he can neither see nor feel a systolic increase in the volume of the left atrium. We also have been unable to demonstrate a greater systolic increase in atrial pressure than may occur in pure mitral stenosis. It might be objected that this is because conditions at operation are abnormal. In the examination of these cases, before operation, however, expansile pulsation of the left atrium has not been detected, nor in the pulmonary capillary tracing have we been able to show a characteristic wave of high pressure coinciding with ventricular systole.

Studies on the form of the systolic heart (Quain, 1929) suggest how the mitral orifice may be guarded from the full effects of the ventricular pressure. " In the contracted left ventricle . . . the two papillary muscles come into contact with one another and the lateral wall of the ventricle comes into contact with the papillary muscles, so that the interpapillary space and the ' inflowing ' part of the ventricle, with the exception of a small space behind the posterior cusp of the mitral valve and the heart wall are obliterated." Fig. 4 (after Quain) shows the anatomical relationship of the structures concerned, and indicates how the inflow portion of the ventricle may be obstructed during ventricular systole.

All these observations indicate that the volume of blood regurgitated through a wide and rigid mitral valve is small in comparison with the capacity of the left atrium and pulmonary veins.

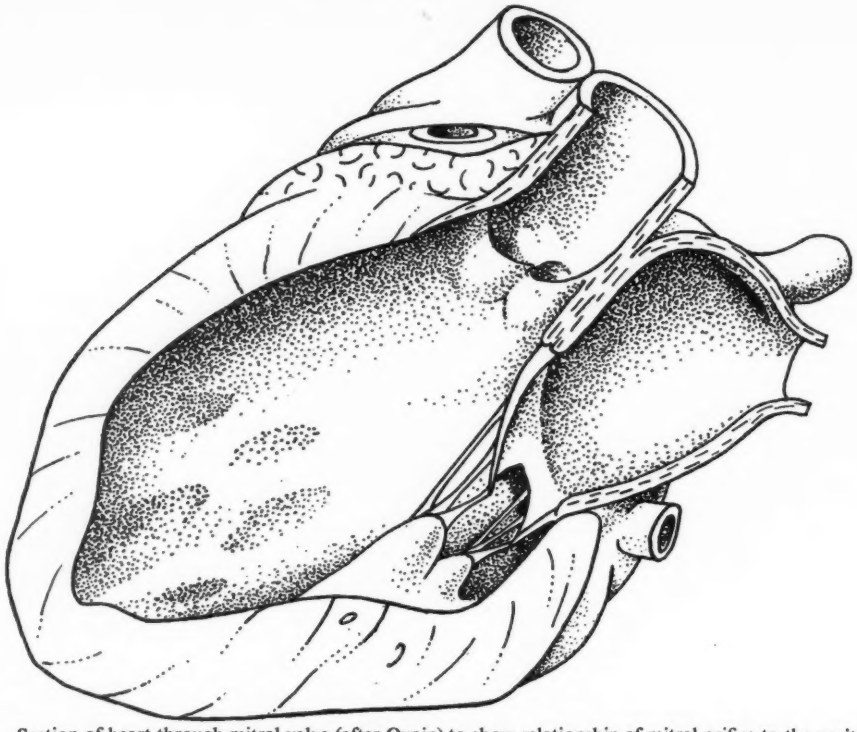

FIG. 4.—Section of heart through mitral valve (after Quain) to show relationship of mitral orifice to the cavity of the left ventricle.

SUMMARY AND CONCLUSIONS

The valves of 96 patients with mitral disease were examined at operation; 61 of them were found to have severe mitral stenosis and no palpable regurgitant stream and were suitable for valvotomy, 9 were found to have larger rigid orifices and a regurgitant stream and were unsuitable for valvotomy. The findings in these two groups before operation are compared. Twenty-six cases with intermediate degrees of stenosis and regurgitation were not used in this comparison.

A " lifting " apical impulse was not found in any of the cases with mitral stenosis alone, whereas it was found in six of eight with wide rigid mitral orifices. All the latter had a loud systolic murmur, but this sign was often present in pure mitral stenosis also. The two groups could not be clearly separated on other clinical findings, nor did electrocardiography, radiology, or cardiac catheterization accomplish this.

The 9 cases with rigidly open valve orifices would readily be classed on pathological examination as examples of mitral incompetence; moreover, the surgeon felt a regurgitant jet of blood in them. The exposed atrium, however, did not show systolic expansion, nor was the systolic rise of atrial pressure greater than that recorded in pure mitral stenosis. These findings indicate that the volume of regurgitant blood is small in comparison with the volume of the left atrium and pulmonary veins. Supporting evidence for this statement is given by the absence of systolic expansion of the left atrium on fluoroscopy, and the absence of differences in the V wave of the pulmonary capillary tracings in the two groups. The explanation is offered that free regurgitation does not necessarily occur through a valve with a rigidly open orifice, because it is guarded during ventricular systole by apposition of the papillary muscles and the ventricular wall.

Dr. David Verel played a large part in the development of the technique used for recording of pressure pulses. The valuable technical assistance of Mr. J. O'Halloran and Mr. P. Sarbinowski is also acknowledged.

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GROSS CALCIFICATION OF THE MITRAL VALVE

BY

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Some degree of calcification of the mitral valve is a common finding at autopsy in advanced rheumatic heart disease. Epstein (1940) reported its presence in 64 out of 148 consecutive post-mortem examinations in amounts varying from that detectable only by microscopy to large calcareous masses. Although the valve leaflets were most often affected, the annulus fibrosus, the chordæ tendineæ, the papillary muscles, and the wall of the left auricle may also be involved. Sometimes gross calcification was confined to only one of these sites, the annulus fibrosus alone being particularly affected in elderly patients with mitral stenosis. With the exception of this group, the degree of calcification tended to correspond with the severity of the other changes due to the rheumatic process.

Present Investigation and Methods

Because of the renewed interest in mitral valvulotomy, it is of some practical importance to consider the clinical features that accompany gross mitral valve calcification, particularly its relation to the duration and severity of the disease, its effects upon the sounds and murmurs, and upon the competence of the mitral valves. These features have been studied in 60 adult patients with mitral stenosis, and evidence of gross valvular calcification. This was defined as a degree of calcification sufficient to be seen by fluoroscopic examination or the presence of craggy masses of calcareous material in the mitral valve at necropsy or at mitral valvulotomy. Calcareous plaques, too small to be seen by fluoroscopy, were sometimes found at valvulotomy or at necropsy. It was considered that these were unlikely to modify the physical signs or alter the function of the mitral valves, so such patients were not included in the grossly calcified group.

One hundred and seventy patients with mitral stenosis without radiological evidence of mitral calcification served as controls. The patients without calcification were unselected; some of those with calcification were specially referred. Patients with aortic stenosis, severe aortic incompetence, hypertension, acute rheumatic carditis, and bacterial endocarditis were excluded.

Clinical and fluoroscopic examinations were performed by the author, and when mitral calcification was considered to be present, and in many of the remainder, an independent fluoroscopic examination was made. Phonocardiograms were taken in many patients, especially when the findings on auscultation were in doubt. In some of the patients, hæmodynamic data obtained by cardiac catheterization and at mitral valvulotomy were available. The technique used for obtaining left auricular pressures at operation has been detailed elsewhere (Wynn *et. al.*, 1952).

Fifty-eight patients had radiological evidence of mitral calcification. In twelve, this was also proven at valvulotomy, and in six at necropsy. Two patients with gross mitral calcification at necropsy were not examined radiologically.

In the 170 patients in whom there was no radiological evidence of mitral calcification, the mitral valve was examined at valvulotomy in thirty-four, and at necropsy in eight. Calcification in these patients was absent or limited to microscopic infiltration or to small plaques.

* This work was started at the Postgraduate Medical School of London.

Results

Age Incidence of Gross Mitral Calcification

The age incidence in decades from 15–75 years is shown in Fig. 1. In the three decades up to forty-five there was a slight preponderance of patients without gross calcification. This was reversed in the three decades after forty-five, but the difference is too slight to suggest that the severity of calcification is closely related to age or to the duration of the disease. Seven patients with gross mitral calcification were under 25 years, the youngest being a girl aged 18 years. The extent to which it may be present in the young is shown by the radiological appearances in a man of 26 years (Fig. 2), and the necropsy appearance in a woman of 28 years (Fig. 3).

FIG. 1.—Shows age incidence of gross mitral valve calcification in decades from 15 to 75 years of age.

Relation of Mitral Calcification to Clinical Severity

To assess the clinical severity, the patients were divided into three grades, using the following criteria.

Grade I.—Patients with no symptoms, or with symptoms only on more than ordinary effort.

Grade II.—Patients able to work normally despite symptoms produced by ordinary activities.

Grade III.—Patients with symptoms at rest or on slight effort, and unable to work or else capable of only light tasks.

Of the patients with gross mitral calcification 15 per cent had only mild symptoms compared with 35 per cent of the control group. Of the former 38 per cent had symptoms of Grade II severity compared with 33 per cent of the control group.

In patients with gross calcification 47 per cent had symptoms of Grade III severity compared with 32 per cent in the control group.

The proportion of patients with severe symptoms in both groups is unduly high because many had been referred for assessment of their suitability for mitral valvulotomy. That 9 patients with gross mitral calcification had few symptoms and more than half were working normally indicates that this process does not closely parallel the clinical severity of the disease.

Hæmodynamic Data

The pulmonary artery and " pulmonary capillary " pressures at rest and after exercise were obtained by cardiac catheterization in all the patients operated upon, and in many of the remaining patients of Grade II and III severity in both groups. The details of this investigation will be presented in a separate communication. There was no significant difference between either pulmonary artery or " pulmonary capillary "

FIG. 2.—Penetrating film in right anterior oblique position to show extensive calcification in the mitral valve in a man of 26 years.

FIG. 3.—Gross calcification in the mitral valve extending on to the chordæ tendineae in a woman of 28 years, with mitral stenosis, who died in cardiac failure. The absence of left ventricular dilatation or hypertrophy suggests that there was no significant mitral reflux in life.

pressures in the two groups. The only noteworthy feature was the demonstration in 4 patients with gross mitral calcification of mean pulmonary artery pressures at rest of 25 mm. Hg or less, which supports the view previously derived clinically that gross mitral calcification may occur in the absence of severe mitral stenosis.

Effect of Gross Calcification on Sounds and Murmurs

The combination of a loud first heart sound, a widely duplicated second sound, a rumbling diastolic murmur and no systolic murmer is well called the mitral rhythm of Duroziez, following this author's classical description in 1862 (Fig. 4). Later, Potain stated that this rhythm was typical of only the middle phase of mitral stenosis when the valve cusps, although thickened and fibrous, were still flexible. If they became rigid and immobilized by calcification the first sound tended to be muffled, systolic murmurs appeared and were often loud, the "opening snap" disappeared and the low-pitched diastolic rumble was replaced by a high-pitched murmur.

The results reported below tend to confirm the accuracy of this observation.

(*i*) *The First Heart Sound.* As the character of the first heart sound in mitral stenosis is greatly modified by the heart rate, the patients were examined reclining and when the pulse rate was between 65 and 90 a minute. Observations were made on the loudness, quality, and palpability of the first heart sound at the apex. These were recorded before the fluoroscopic examination.

The first sound was called snapping when it was accentuated, rather high-pitched, and peremptory. The vibrations were usually palpable often over a localized area at or near the apex. A snapping first sound occurred in 20 per cent of the patients with gross calcification and in 50 per cent of the controls (Table I).

A loud, but dull or blurred, first sound, whose vibrations were much less frequently palpable—and then

often over a diffuse area of the præcordium—was heard in 35 per cent of the calcified group, and in 32 per cent of the uncalcified group. Whether loud or snapping, the first sound was palpable in 33 per cent of the calcified group compared with 68 per cent of the controls.

The first sound was normal or obscured by a systolic murmur in 45 per cent of the patients in the calcified group and in 18 per cent of those without evidence of gross valvular calcification. With tachycardia, however, the first sound was frequently loud, sharp, and readily palpable in many of the patients with mitral calcification.

(*ii*) *Systolic Murmurs.* Systolic murmurs at the apex were graded according to intensity as faint, medium, and loud (Table I). These were twice as frequent in the calcified group, and were more often loud. Nevertheless, one in five patients with gross valvular calcification had no systolic murmur. In one patient

TABLE I

COMPARISON OF PHYSICAL SIGNS PRODUCED BY CALCIFIED AND UNCALCIFIED VALVES

	First heart sound (%)				Mitral systolic murmurs (%)				Opening snap (%)
	Snapping	Loud	Normal or obscured	Palpable	Faint	Medium	Loud	Total	
Calcified	20	35	45	33	10	28	28	66	48
Uncalcified	50	32	18	68	10	15	17	42	82

without a systolic murmur both cusps of the mitral valve were found to be extensively calcified at necropsy, and there was a calcareous mass 10 mm. in diameter extending from the base to the free margin of the postero-medial cusp.

(*iii*) *The "Opening Snap."* An added protodiastolic sound in the cardiac cycle which had most or all of the following features, was regarded as an "opening snap" (Wolferth and Margolies, 1932).

(*a*) Distinctly separate from the second sound even during expiration.

(*b*) Heard widely, but never loudest at the base.

(*c*) Loudest at a point between the apex and the left sternal border, but sometimes very well heard at the apex when the diastolic murmur was not loud or long.

(*d*) Often preceding the diastolic rumble by an audible gap.

(*e*) Often having a superficial clicking quality.

Clinical differentiation between a widely split second sound, an "opening snap," and a loud third heart sound was sometimes impossible. The phonocardiogram was then used to help in identification. When the interval between the two sounds was less than 0·06 sec., in the absence of right bundle branch block at pulse rates under 85 a minute, it was regarded as a split second sound. When the interval was between 0·06 and 0·12 sec. the added sound was classed as an "opening snap." With tachycardia the "opening snap" may approach as close as 0·05 sec. to the second sound, when it cannot be distinguished from a split sound due to asynchronous closure of the pulmonary and aortic valves. When the heart rate slows, however, or after an unduly long diastole if there is auricular fibrillation, the interval may increase to more than 0·06 sec. if the added sound originates in the mitral valve. In many cases, the difficulty of identification was resolved by recording both a split second sound and an "opening snap" in the same cycle (Fig. 5). This was possible more often when the record was taken in varying phases of respiration.

The jugular phlebogram was found to be a useful reference tracing in distinguishing between the "opening snap" and a third heart sound. The latter occurs after the peak of the "V" wave of the phlebogram and usually more than 0·12 sec. after the second sound.

An "opening snap" was present on auscultation or clearly demonstrated by phonocardiography in 48 per cent of the calcified group compared with 82 per cent of the controls. In many of the control patients this sound had a sharp clicking quality, which was rarely present in the patients with gross mitral calcification. Although the mechanism of production of this sound is unknown, the evidence reviewed by Wolferth and Margolies (1932) that it is produced by the opening movement of the mitral valves is good. Its persistence in the presence of extensive calcification may be due to part of the valve cusps and chordæ tendineæ being uncalcified and flexible (Wolferth and Margolies, 1937).

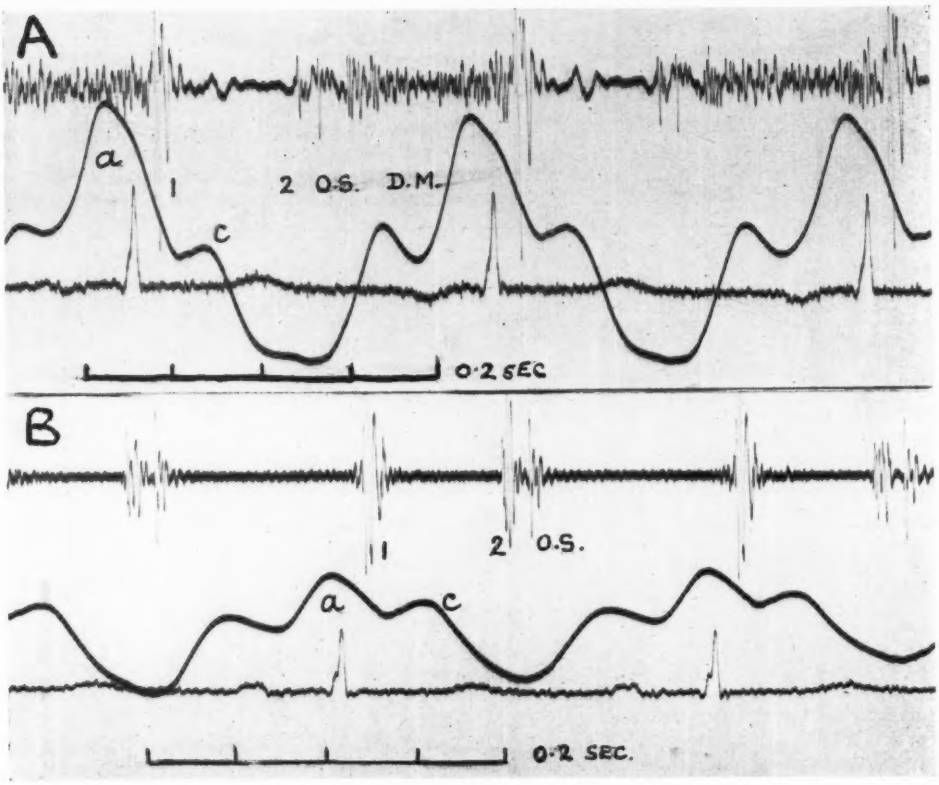

FIG. 4.—Rhythm of Duroziez in a patient with no valvular calcification at mitral valvulotomy, showing loud first sound, no systolic murmur, widely duplicated second sound, and rumbling diastolic murmur with mid and late diastolic accentuation. (A) phonocardiogram at apex. (B) phonocardiogram at left sternal border in fourth left intercostal space.

P.C. Phonocardiogram. J.V.P. Jugular phlebogram. E.C. Electrocardiogram.

(*iv*) *The Diastolic Murmur.* No difference in duration, intensity or pitch of the diastolic murmur could be detected between the two groups by the methods used in this investigation.

A pure rhythm of Duroziez was heard in 28 out of 42 patients who had little or no calcification at operation or at necropsy (Fig. 4); in 18 patients with gross calcification at operation or at necropsy it was present only three times. In one of these patients the calcified mass was confined to the annulus fibrosus, and in another the calcification was thought by the surgeon to involve mainly the floor of the auricle while the cusps themselves remained flexible.

Effect of Calcification on the Incidence of Mitral Incompetence.

No attempt was made to diagnose slight degrees of mitral incompetence in this study. It was considered, however, that significant mitral regurgitation in the presence of mitral stenosis could be detected by the following criteria.

(1) A mitral systolic murmur with clinical evidence of an enlarged or hyperdynamic left ventricle, shown by a localized, unduly forceful apex beat accompanied by enlargement of the left ventricle and left auricle on fluoroscopy. Patients with significant aortic valve disease or hypertension were excluded.

(2) In the absence of a characteristic apical impulse a diagnosis of left ventricular enlargement on fluoroscopy was made only when the enlargement appeared considerable.

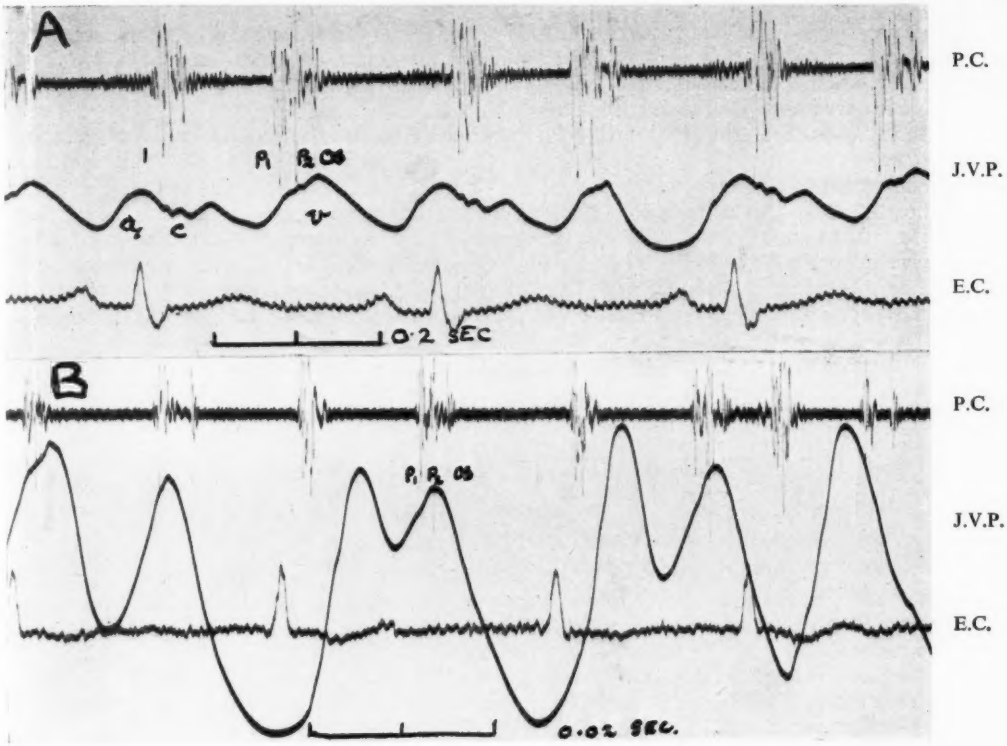

FIG. 5.—(A) Phonocardiogram showing a split second sound and an " opening snap " in each cardiac cycle. (B) Phonocardiogram showing phasic splitting of the second sound with an " opening snap." Phonocardiogram at left sternal border in fourth left intercostal space.

P.C. Phonocardiogram. J.V.P. Jugular phlebogram. E.C. Electrocardiogram.

(3) When the left auricle was very large or aneurysmal.

(4) Electrocardiographic evidence of left ventricular hypertrophy when it occurred.

Systolic expansion of the left auricle (Heim de Balsac *et al.*, 1949), when it occurred in the absence of criteria already discussed, was not accepted as evidence of mitral incompetence. It is due presumably to the sharp rise in auricular pressure during ventricular systole, which can be frequently demonstrated at valvulotomy, especially if there is auricular fibrillation (Wynn *et al.*, 1952).

Froment *et al.* (1950) suggest that systolic expansion of the left auricle is due to retropulsion of the mitral valve cone into the left auricle during ventricular contraction. Support for this view was obtained in the present study, for, on fluoroscopy in the right anterior oblique position, the movement of mitral calcification was frequently seen to be backwards and synchronous with the movements of the border of the left auricle during ventricular systole.

The incidence of mitral incompetence judged by the above criteria was 40 per cent in the calcified group and 21 per cent in the control group. More direct evidence that the mitral valves may be competent, although grossly calcified, was obtained at operation. In 12 patients with gross calcification at operation a regurgitant jet was felt in six, while in 34 of the control group a regurgitant jet was felt in eight patients.

The left auricular pressures obtained at operation were of more limited value than the surgeon's findings in demonstrating mitral incompetence (Wynn *et al.*, 1952). Nevertheless, they supported the view that in half the patients with gross calcification of the valve there was no significant mitral incompetence.

Discussion

These results indicate that gross calcification of the mitral valve, occurring as a complication of rheumatic heart disease, has no striking connotations in either a clinical or hæmodynamic sense, except in relation to mitral regurgitation. Although occurring more frequently in the older age groups and in patients with severe symptoms, the differences were not great. Moreover, it may occur in young patients and in those with no clinical or hæmodynamic evidence of severe rheumatic heart disease.

When gross mitral calcification is present the classical auscultatory rhythm of Duroziez is not often heard, but to what extent this is due to associated factors such as reduced mitral blood flow, congestive cardiac failure, and mitral incompetence, it is difficult to say. When the calcification is largely confined to the region of the annulus fibrosus or to the floor of the auricle, leaving the mitral leaflets flexible, however, the rhythm of Duroziez may be present.

Although the true incidence of mitral incompetence is difficult to determine, the clinical and operative evidence in this survey suggests that significant mitral incompetence occurs in about half the patients with gross valvular calcification, being twice as frequent as in the controls. How closure of the mitral valves is achieved when the valve cusps and ring are grossly calcified is obscure. Lutembacher (1950) attributes a piston-like action to the hypertrophied papillary muscles which seals off the mitral orifice during ventricular systole. The observation that mitral calcification is thrust backwards into the auricle at the onset of ventricular contractions supports this view.

Summary and Conclusions

The relation of gross valvular calcification in mitral stenosis to age and clinical severity, and its effect upon the auscultatory physical signs and upon the function of the mitral valves has been studied. There were 60 patients with gross mitral calcification and 170 controls.

The patients with gross mitral calcification were only slightly older, 86 per cent being under 55 years compared with 92 per cent of the controls.

Although more of the patients with gross calcification had clinical and hæmodynamic evidence of severe mitral valve disease, 15 per cent had only mild symptoms and over half were able to work normally.

In the presence of gross mitral calcification the first heart sound was rarely snapping or palpable at pulse rates under 90 a minute. In 80 per cent a mitral systolic murmur was present, and this was often loud. An opening snap was less often heard in these cases and was rarely loud or clicking, but the diastolic murmur appeared to be unaffected.

The diagnostic value of these observations is limited because of the many variables involved.

Significant mitral incompetence was thought to be twice as common in the patients with gross mitral calcification compared with the controls.

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THE MECHANISMS OF ADAPTATION TO A CENTRAL VENOUS-ARTERIAL SHUNT

BY

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A central venous-arterial shunt consists essentially of the transfer of a proportion of the venous blood directly into the systemic arterial tree without passage through the pulmonary capillaries. Cyanosis of central origin is the major clinical manifestation and characteristically this is deepened by exertion and cannot be abolished by inhalation of pure oxygen. Some loss of exercise tolerance is invariably present, and when a high proportion of the venous return by-passes the pulmonary capillaries disability is severe and is associated with poor physical development.

While a great variety of congenital cardiac abnormalities may be accompanied by a central venous-arterial shunt from infancy, the tetralogy of Fallot is encountered most frequently. If the shunt first appears in later life it is often the result of progressive pulmonary hypertension superimposed upon a large septal defect. Pulmonary arterio-venous aneurysms are a rare cause of the condition, and are usually found with hereditary telangiectasia.

In recent years, wide interest in cyanotic congenital heart disease has been stimulated by the successful surgical treatment of the tetralogy of Fallot (Blalock and Taussig, 1945; Brock and Campbell, 1950). Accurate pre-operative diagnosis is essential, and physiological investigation by right heart catheterization has proved invaluable in doubtful cases (Bing *et al.*, 1947*a* and *b*; Cournand *et al.*, 1949; Holling and Zak, 1950). The data obtained in this way have made it possible to study the underlying mechanisms of adaptation to a central venous-arterial shunt (Bing *et al.*, 1948; Burchell *et al.*, 1950; Ernsting and Shephard, 1951).

The purpose of this study is to evaluate the mechanisms of adaptation to a central venous-arterial shunt in the light of observations on patients with this condition.

METHODS

Thirty-six patients were studied, of whom 32 had congenital heart disease and 4 pulmonary arterio-venous aneurysms. The cases were unselected, a central venous-arterial shunt being the only criterion for inclusion. Sex distribution was approximately equal and their ages ranged from 5 to 35 years. The severity of the disability varied from slight to almost complete incapacity.

Pulmonary stenosis was confirmed by measurement of pulmonary arterial and right ventricular pressures in 14 of the 18 cases with Fallot's tetralogy, and in the one with pulmonary stenosis and an atrial septal defect. Eisenmenger's syndrome was diagnosed in 6 patients after demonstrating a central venous-arterial shunt with gross rise of pulmonary arterial pressure; these probably included cases of septal defect with reversed shunt. Exploratory thoracotomy supported the diagnosis in 15 and in 2 it was confirmed at necropsy.

Diagnostic right-heart catheterization was employed in all but two of the series. Tea and toast was allowed two hours before the investigation, performed by the usual technique with the patient in the supine resting state under light barbiturate or rectal avertin sedation. Mixed venous blood samples were taken from the right atrium in all but one in whom anomalous pulmonary veins entering the superior vena cava necessitated use of the inferior vena caval sample. Arterial blood samples were taken through an indwelling brachial arterial needle during catheterization or by femoral arterial puncture immediately the catheter

had been withdrawn. Intracardiac and pulmonary arterial pressures were measured with a saline manometer or mechano-electronic transducing manometer (Cumming *et al.*, 1950) employing a Cossor oscilloscope and camera, and in later instances a Sanborn polyviso oscillograph.

The effect of exercise was studied in five cases, a bicycle ergometer being mounted to the foot of the screening table so that the patient could pedal whilst lying supine. The work which each could readily perform for five minutes without undue distress was determined before the investigation, and the rate of work was kept constant by synchronizing the ergometer with an electric motor. Approximately two minutes was allowed for stabilization, and brachial arterial and right atrial blood samples were taken simultaneously during the collection of expired air, which averaged two minutes.

The methods of Van Slyke and Neill were employed for gas analysis of blood samples; *p*H and pCO_2 were not estimated. Oxygen consumption at rest and during standard exercise tests, minute ventilation, and R.Q. were estimated from Douglas bag collections of expired air. When a Tissot spirometer became available it was used as a reservoir and means of measuring inspired volumes, whilst Douglas bags were still employed for expired air collection; this was found preferable to collecting directly into the Tissot because it avoids the delay while the spirometer dead-space is washed out with expired air. Gas samples were analysed in the Sleigh apparatus, whose accuracy compares favourably with that of the Haldane. Gas volumes were corrected for temperature and barometer; oxygen consumption, etc. being recorded as dry volumes at 760 mm. Hg, 0° C. (NTP), and ventilation rates as volumes of saturated gas at 37° C. and ambient pressure (BTPS).

Circulatory instability, frequently present in cyanotic heart disease, makes it desirable to investigate cardiac and respiratory functions simultaneously when their interrelationship is a subject of study. When technical difficulties prevented this the independent investigations were made, as far as possible, under the same conditions.

Blood flow was estimated by application of the direct Fick principle (Fick, 1870).

Effective pulmonary blood flow, i.e. the amount of mixed venous blood entering the pulmonary capillary bed, both directly and by way of collateral vessels, is given by the formula:

$$\frac{\text{O}_2 \text{ consumption (ml./min.)}}{(\text{pulmonary venous O}_2 \text{ content} - \text{mixed venous O}_2 \text{ content})} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The oxygen content of blood leaving the lungs (pulmonary venous blood) was presumed to be 95 per cent of the blood oxygen capacity in all but one subject in whom catheterization of a pulmonary vein made direct estimation possible; in formula (1) one can therefore substitute ($0{\cdot}95 \times \text{O}_2$ capacity) for pulmonary venous O_2 content.

Systemic blood flow, i.e. the amount of blood perfusing the systemic capillary bed, is given by the formula:

$$\frac{\text{O}_2 \text{ consumption (ml./min.)}}{(\text{arterial O}_2 \text{ content} - \text{mixed venous O}_2 \text{ content})} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The central venous-arterial shunt, expressed as a percentage of the systemic flow, is given by the formula:

$$100 - \frac{(\text{arterial O}_2 \text{ content} - \text{mixed venous O}_2 \text{ content})}{(0{\cdot}95 \times \text{O}_2 \text{ capacity} - \text{mixed venous O}_2 \text{ content})} \times 100 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Arterial and mixed venous blood oxygen tensions were calculated from the oxygen dissociation curve for human blood at *p*H 7·40 based upon the data of Dill (1944).

Mean systemic capillary oxygen tension, taken to represent " the oxygen pressure, which, if it prevailed throughout the entire length of all the capillaries of the body, would not alter the quantity of oxygen diffusing under actual physiological conditions " (Houston and Riley, 1947), was estimated according to Barcroft's suggested approximation (1934) and is given by the formula:

$$\text{Mixed venous } pO_2 + (\text{arterial } pO_2 - \text{mixed venous } pO_2)/3 \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Respiratory studies on patients of this series have shown that the resting oxygen uptake lies within the predicted range of normality; therefore, to facilitate more detailed analysis of circulatory function, the observed arterio-venous oxygen difference has been employed to express the systemic and effective pulmonary blood flows of each patient as a percentage of the average normal resting value, where an arterio-venous oxygen difference of 4·40 ml. per 100 ml. of blood has been taken as the normal value for both systemic and effective pulmonary flow: Blood flow (per cent of normal) equals:

$$\frac{4{\cdot}40}{\text{A-V O}_2 \text{ diff.}} \times 100 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The published findings of Bing *et al.* (1947*b*) upon 36 patients with the tetralogy of Fallot have also been analysed by these methods, and the results incorporated in the later section of this work. Their findings from blood-gas analysis follow the same pattern as our own, but we have been unable to confirm the depression of resting oxygen uptake observed in many of their cases.

The influence of the hæmoglobin content of the blood (where 100 per cent hæmoglobin is equivalent to

20 volumes per cent O_2 capacity) upon the percentage oxygen saturation of mixed venous blood and the mean systemic capillary oxygen tension has been predicted at different levels of effective pulmonary blood flow by application of the following formulæ, which presume a normal resting oxygen uptake and normal resting systemic blood flow: *Effective pulmonary blood flow* (percentage of normal) equals:

$$\frac{4{\cdot}40}{O_2 \text{ capacity} \times \frac{(95 - \text{percentage } O_2 \text{ sat. mix. ven. blood})}{100}} \times 100 \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Percentage O_2 sat. arterial blood equals:

$$\text{Percentage } O_2 \text{ sat. mix. ven blood} + \frac{4{\cdot}40}{O_2 \text{ capacity}} \times 100 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Mean systemic capillary oxygen tension is then predicted from formula (4).

Employing formula (6), curves have been plotted (Fig. 3) to show the relationship between effective pulmonary blood flow and the percentage oxygen saturation of mixed venous blood at different hæmoglobin levels. Employing formulæ (6), (7), and (4), curves have been plotted (Fig. 2) to show the relationship between effective pulmonary blood flow and mean systemic capillary oxygen tension at different hæmoglobin levels.

The methods used in the analysis of respiratory function are discussed in the section on respiratory behaviour.

Results

Details of the findings are shown in Table I. Oxygen capacity of the blood showed a wide variation with a mean of $24{\cdot}1 \pm 0{\cdot}9$ vols. per 100 ml. Arterial oxygen saturation was invariably depressed, with a mean value of 76 per cent. Arterial carbon dioxide content was below normal in every case. Mixed venous oxygen saturation was also reduced in most patients.

The systemic arterio-venous oxygen difference lay within the limits of normal in all but six patients and the mean value of $4{\cdot}3 \pm 0{\cdot}2$ vols. per 100 ml. approximates closely to the normal.

The effective pulmonary arterio-venous oxygen difference lay above the upper limit of normal in all but four cases, and the mean value of $8{\cdot}94 \pm 0{\cdot}55$ volumes per 100 ml. is equivalent to an effective pulmonary flow 49 per cent of the normal. The venous-arterial shunt showed wide variation with a mean value of 47 per cent of the systemic blood flow. Mean systemic capillary oxygen tension was consistently depressed and the mean value of $35{\cdot}2 \pm 1{\cdot}0$ mm. Hg is 20 mm. below the average normal value.

Comparison of the effective pulmonary arterio-venous oxygen difference in patients with Fallot's tetralogy and Eisenmenger's syndrome shows no significant difference; therefore, the size of the effective pulmonary flow is no guide to the pulmonary arterial pressure, since it may be greatly curtailed in the presence of extreme pulmonary hypertension.

The mean values for both systemic and effective pulmonary arterio-venous oxygen differences were lowest in patients with congenital pulmonary telangiectasia. Therefore, as a group, these cases showed the least depression of effective pulmonary flow with a moderate but constant increase in systemic flow.

There was evidence of gross hæmodynamic instability during investigation of three patients with Fallot's tetralogy. In two (Cases 4 and 14), considerable fluctuation of exercise tolerance was noted clinically, and cyanotic episodes with loss of consciousness frequently occurred in the latter. Both exhibited increasing cyanosis and sinus tachycardia during investigation, and intra-arterial pressure records taken in Case 14 showed marked reduction of the systemic blood pressure. The low arterial oxygen saturations observed, produced by a large central venous arterial shunt in each case, were inconsistent with the moderate reduction of effective pulmonary flow. In the third (Case 6) exercise tolerance showed little variation and the hæmodynamic instability was probably due to leaving the cardiac catheter for too long (10 to 15 minutes) within the stenosed right ventricular outflow tract.

The remainder showed no evidence of instability during investigation, and the values obtained are considered representative of their normal resting state.

TABLE I

ARTERIAL OXYGEN AND CARBON DIOXIDE PERCENTAGES AND VENO-ARTERIAL SHUNT

Case No.	Oxygen capacity (vol./100 ml.)	Arterial CO_2 content (vol./100 ml.)	Arterial O_2 percentage saturation	Mixed venous percentage O_2 saturation	Mean systemic capillary oxygen tension (mm. Hg)	Effective pulmonary A-V O_2 difference	Systemic A-V O_2 difference	V-A shunt percentage of systemic flow
				Tetralogy of Fallot				
1	23·6	—	—	53	—	9·9	—	—
2	22·8	40·9	81	59	36	8·2	5·1	38
	23·3	42·3	77	58	34	8·6	4·4	48
3	24·5	40·7	76	58	34	9·0	4·3	52
4	19·5	40·8	72	62	34	6·5	1·8	72
5	26·1	37·7	—	59	—	9·4	—	—
6	28·0	37·0	27	20	14	20·9	1·9	91
	—	36·8	76	—	—	—	—	—
7	21·7	35·5	82	65	39	6·4	3·7	42
8	30·4	30·4	81	64	38	9·5	5·3	44
9	18·2	36·7	91	65	43	5·4	4·7	12
10	19·7	43·9	87	65	41	5·8	4·3	26
11	31·9	38·1	73	61	34	10·7	3·7	65
12	23·4	40·2	75	63	36	7·4	2·7	64
13	21·7	38·5	84	66	40	6·4	4·1	36
14	15·8	42·6	66	65	—	4·8	—	—
15	27·5	39·1	65	57	31	10·5	2·2	79
16	24·5	38·3	81	53	37	10·2	6·8	33
17	29·3	37·1	79	69	39	7·7	3·0	61
18	32·3	32·9	82	68	40	8·5	4·7	45
Mean	24·4	38·5	78	62	37	8·0	4·0	47
S.D.	4·3	3·2	7	4	3	1·9	1·3	19
S.E.M.	1·0	0·8	2	1	1	0·5	0·4	5
				Eisenmenger complex				
19	23·4	39·3	79	59	35	8·5	4·8	43
20	16·1	—	75	55	33	6·5	3·3	49
21	23·7	—	74	47	30	11·3	6·5	43
22	13·6	39·4	75	46	30	6·7	4·0	40
23	28·6	34·2	80	64	37	8·9	4·8	46
24	27·2	38·3	88	68	42	9·5	7·5	21
Mean	22·3	37·7	81	56	35	8·6	5·1	40
S.D.	6·1	2·9	3	8	3	1·9	1·2	3
S.E.M.	2·7	1·72	1	3	1	0·9	0·5	1·5
				Pulmonary telangiectasia				
25	21·1	43·7	90	71	46	5·0	3·4	21
26	16·5	43·5	72	49	30	7·6	3·8	50
27	29·0	36·1	81	69	39	7·6	3·5	54
28	14·2	46·3	64	48	28	6·7	2·4	64
Mean	20·2	42·4	77	59	36	6·7	3·4	47
S.D.	6·5	4·4	11	12	8	1·2	0·7	18
S.E.M.	3·3	2·2	5	6	4	0·6	0·3	9
				Miscellaneous				
29	28·8	44·5	59	41	25	15·5	5·2	67
30	27·9	36·9	75	56	33	10·9	5·4	50
31	30·4	34·6	48	35	22	18·3	3·9	78
32	24·3	40·9	84	66	39	7·6	4·4	42
33	26·3	—	—	45	—	13·2	—	—
34	33·9	31·6	69	50	29	15·4	6·5	58
Mean	28·6	37·7	67	48	30	13·5	5·1	59
S.D.	3·4	5·1	14	11	7	3·8	0·9	14
S.E.M.	1·4	2·3	6	4	3	1·5	0·4	6
				Mean values for the whole series				
Mean	24·2	38·7	76	58	35	8·9	4·3	47
S.D.	5·2	3·8	9	9	5	3·1	1·2	16
S.E.M.	0·9	0·7	2	1	1	0·5	0·2	3

The results of the respiratory function tests are discussed in the sections devoted to respiratory behaviour.

Discussion

A central venous-arterial shunt impairs the efficiency of oxygen transport from lungs to tissue in two ways, both of which are independent of the precise cardiac abnormality: (1) the patient's capacity to absorb oxygen is limited by the reduced venous inflow to the lungs; and (2) the oxygen tension of arterial blood supplied to the tissues is depressed by venous admixture.

Theoretically, adaptation to the state of subnormal effective pulmonary blood flow could occur by reduction of oxygen utilization, increase in arterio-venous oxygen difference (where " arterio " refers to pulmonary venous blood), and increase in hæmoglobin concentration. Increase in systemic blood flow can be regarded as an adaptation only when accompanied by increase in effective pulmonary flow. Adaptation by depression of oxygen content of mixed venous blood is restricted by the necessity of maintaining capillary oxygen tension at a level sufficient to enable oxygen to diffuse into the tissues. Extreme polycythæmia carries the disability of high viscosity.

Resting Oxygen Consumption

The question must first be faced as to the normality or otherwise of basal oxygen consumption in these conditions. In conformity with previous work (Holling and Zak, 1950; Burchell *et al.*, 1950; Ernsting and Shephard, 1951) it was found to be normal, but Bing *et al.* (1947*b*) in their pioneer survey of 36 cases of Fallot's tetralogy, found low figures for B.M.R. in 34, with values as low as 48 and 46 per cent. They attribute this depression to chronic anoxia (though in fact there is little evident correlation within their series between B.M.R. and arterial oxygen saturation), and they stated their intention of publishing evidence that the effect of the Blalock operation was to elevate the B.M.R. where it was depressed. Their results and inferences imply such a bankruptcy of the oxygen economy as would make it idle to discuss adaptations to anoxia in this or related conditions.

In this series three considerations prevented estimates of what might be represented as B.M.R. These were: (1) the frequent discrepancy between actual and apparent age, which would render suspect the normal standard for heat production; (2) the extreme instability of R.Q. level which marks these cases (and may be due to a predominance in them of the anoxic stimulus to respiration permitting excessive irregularities of ventilation); and (3) the likelihood that those precautions necessary to ensure basal conditions in adults would have the reverse effect on apprehensive children. In the main these factors would tend to raise apparent B.M.R.; and since no specific measures to overcome their effect seems to have been taken by Bing's group, their results are the more surprising.

Instead of B.M.R. determinations on these cases (which were thought likely to be misleading on these grounds) respiratory exchange was determined under near-basal conditions standard in this laboratory. Comparison of the results was therefore possible with those of a control group from records selected only by the exclusion of known cases of anoxæmia or metabolic disorder. Age and sex differences were taken into account by multiplying each observed oxygen consumption in both groups by a factor that in effect projected it into an arbitrary standard age (18) and sex (male). The factor was obtained from the Boothby and Sandiford (1920) revision of Dubois' tables for normal heat production at all ages in each sex, the figure appropriate to the individual being divided by the figure for a male of 18 years.

Results. The composition of the groups and the significance of the differences between them are summarized in Table II. The average observed oxygen consumption figures for the cyanotic group are significantly higher than the corresponding control averages; but with the age influence eliminated in the standardized figures the differences though unchanged in sign are far below the accepted significance level. Had our cyanotic group been divided into Fallot cases and others, the eleven Fallot cases would give an average standardized uptake of 155·6 ml. of oxygen per minute which is, in fact, closer to the whole-group average than the male and female averages show.

In five of the cases of Fallot's tetralogy the oxygen consumption was again measured after Blalock operation, and in none was the change significant. Oxygen consumption rose in 4 patients on whom data were obtained two to three weeks after operation, but in each case the result was a more abnormal figure. Approximately three months after operation, however, all five had figures nearer to the control averages than before operation, and this change represented a fall in four cases and a rise in one.

TABLE II

COMPARISON OF MEAN OXYGEN CONSUMPTION AT REST IN (A) 18 CASES OF CYANOTIC CONGENITAL HEART DISEASE, AND (B) 23 ORDINARY HOSPITAL PATIENTS WITHOUT CYANOSIS

Group		No. of subjects	Age		Resting O_2 uptake (c.c./M²/min.)					
					Observed			Standardized to age 18, male sex		
			Mean	Range	Mean	S.D.	Range	Mean	S.D.	Range
A										
Cyanotic congenital cardiac disease	♂	11	19·2	7–33	164·2	±26	126–220	158·1	±16	138–181
	♀	7	13·5	7–35	160·3	±24	130–190	154·9	±22	122–178
	♂+♀	18	17·0	7–35	162·7	±25	126–220	156·7	±17	122–181
B										
Subjects free from arterial anoxæmia	♂	13	36	11–62	143·5	±16	121–188	153·4	±10	138–168
	♀	10	36	24–48	127·4	±8	118–141	153·5	±10	136–166
	♂+♀	23	36	11–62	136·5	±17	118–188	153·4	±9	136–168

		♂	♀	♂+♀
Mean observed O_2 uptake	Diff. A–B / S.E. diff.	$\frac{20·7}{9·0}=2·30$	$\frac{32·9}{9·5}=3·46$	$\frac{26·0}{6·9}=3·77$
Mean standardized O_2 uptake	Diff. A–B / S.E. diff.	$\frac{4·7}{5·6}=0·84$	$\frac{1·4}{8·9}=0·16$	$\frac{3·3}{5·7}=0·58$

INCREASE IN HÆMOGLOBIN

In 32 patients investigated by cardiac catheterization the effective pulmonary blood flow has been expressed as a percentage of the average normal value (formula 5), and the figures obtained plotted against their oxygen capacities. The findings in 36 cases of Fallot's tetralogy reported by Bing *et al.*, 1947*b*, have been similarly treated. The results are shown in Fig. 1. A highly significant negative correlation exists for each group (personal series (32), r equals 0·894; Bing's series (36), r equals 0·917; combined series (68), r equals 0·882). These statements are based upon the evidence that the resting oxygen consumption is normal.

The size of the effective pulmonary flow is then expressed by the reciprocal value of its arterio-venous oxygen difference; since the pulmonary venous oxygen content is taken to be 95 per cent of the oxygen capacity, the arterio-venous difference then becomes a function of the percentage oxygen saturation and the oxygen capacity of the mixed venous blood (formulæ 6).

When the effective pulmonary blood flow is diminished, oxygen uptake from the lungs can only be maintained by a proportionate increase in the oxygen absorptive capacity of the mixed venous blood, and this can be achieved either by reduction of its oxygen saturation or increase of its oxygen capacity (i.e. hæmoglobin content) or a combination of the two. Reduction of oxygen saturation is the obvious and immediate method of compensating for decreased flow. The relationship which must exist between effective pulmonary flow and oxygen saturation (as percentage) of mixed venous blood, to permit a normal supply of oxygen to the tissues has been predicted (formula 6) and plotted in Fig. 3. When the oxygen-carrying power of the blood is normal (100 per cent hæmoglobin equivalent to 20 vols. O_2 per 100 ml.) it is apparent from the shape of the curve that this mechanism alone adequately compensates for moderate reduction of the flow, but severe limitation would necessitate a fall in venous oxygen saturation to levels probably incompatible

with normal metabolism. Thus reduction of effective pulmonary flow to three-quarters of the average normal value is met by a fall of venous saturation from 73 to 68 per cent, while with a half-normal flow venous saturation falls to 53 per cent, and one-quarter of the normal necessitates a saturation of only 11 per cent. Some additional mechanism is clearly essential if a workable capillary O_2 tension is to be maintained at low rates of pulmonary blood flow.

The influence of the oxygen-carrying power of the blood upon this relationship is shown by curves plotted for hæmoglobin values of 75, 125, 150, 175, and 200 per cent. It is apparent that decreased hæmoglobin depresses the normal curve and shifts it to the left; increased hæmoglobin

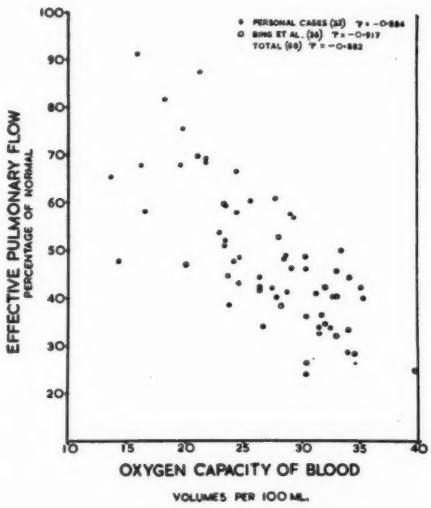

FIG. 1.—The relationship of effective pulmonary flow to the oxygen capacity of the blood.

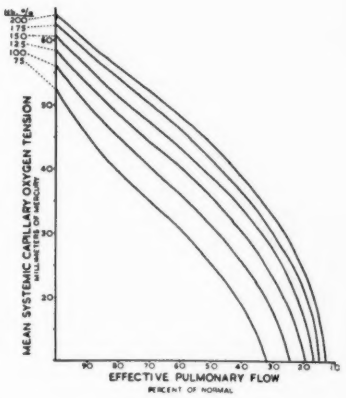

FIG. 2.—Curves showing the effect of different hæmoglobin levels on the relationship of the mean systemic capillary oxygen tension and the effective pulmonary flow (see Fig. 3).

elevates the curve and shifts it to the right, thereby delaying the point at which a precipitous fall in venous saturation must occur. An increased hæmoglobin produces only a slight elevation of venous saturation when the flow is normal or moderately reduced, while the effect on the saturation of hæmoglobin increment is progressively enhanced as the flow diminishes; thus, when the flow is three-quarters of the normal, hæmoglobin increments from 100 to 125, 150, and 175 per cent raise the venous saturation from 68 per cent to 73, 76, and 78 per cent respectively, while the same increments raise the saturation from 11 per cent to 27, 38, and 47 per cent respectively when the flow is reduced to one-quarter of the normal. It is clear, moreover, that there is a decreasing gain in venous saturation with each successive equal increment of hæmoglobin.

In Fig. 3 the observed percentage saturation of mixed venous blood has been plotted against the effective pulmonary blood flow in 68 patients and superimposed upon the predicted relationships for different hæmoglobin values, thus demonstrating that increased hæmoglobin does, in fact, prevent gross depression of venous saturation when the effective flow is greatly reduced.

It follows from this analysis that the resting oxygen uptake is maintained in the presence of a reduced effective pulmonary blood flow by two complementary mechanisms—(1) reduced percentage oxygen saturation of mixed venous blood and (2) increased hæmoglobin content. It is suggested that their integration determines the negative correlation between effective pulmonary blood flow and oxygen capacity of the blood.

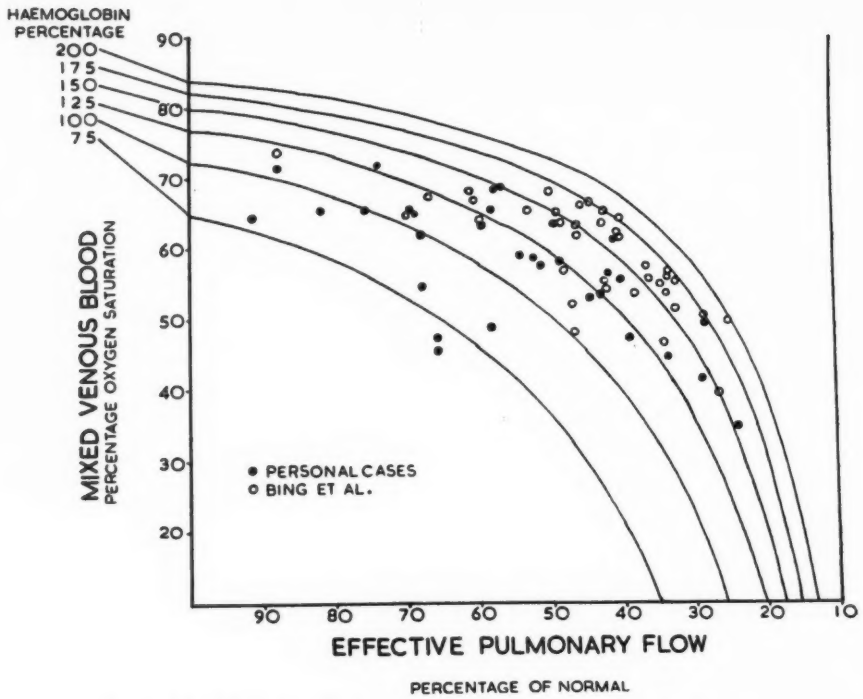

FIG. 3.—The effect of varying hæmoglobin percentages on the relationship between the percentage of oxygen saturation in mixed venous blood and the effective pulmonary flow.

TISSUE OXYGEN TENSION

The mean systemic capillary oxygen tension and the consequent pressure gradient between capillary and cell govern the diffusion rate upon which depends the oxygen tension prevailing in the tissues; the diffusion gradient is relatively constant under the stable conditions of resting oxygen requirements and thus capillary and tissue oxygen tensions have a linear relationship.

Arterial oxygen tension is greatly reduced by a central venous-arterial shunt. The normal values for arterial oxygen saturation and tension lie upon the flat upper portion of the oxygen dissociation curve and therefore a small reduction of saturation—consequent upon venous admixture—is accompanied by considerable reduction of tension. On the other hand, the normal values for mixed venous oxygen saturation and tension lie upon the steep central portion of the dissociation curve and an equivalent reduction of venous saturation produced a much smaller fall in tension. Consequently, the gradient of oxygen tension between arterial and mixed venous blood is greatly reduced by the shunt, and the mean systemic capillary oxygen tension lies very close to that of mixed venous blood. Clearly, the shape of the normal oxygen dissociation curve is most important in preventing profound depression of tissue oxygen tension in these cases (Bing *et al.*, 1948; Ernsting and Shephard, 1951) but this factor is fundamental rather than adaptive since it entails no modification of a normal physiological relationship.

As shown, the percentage oxygen saturation of mixed venous blood is determined by its oxygen-carrying power and the size of the effective pulmonary blood flow, and may be predicted from

any relationship between these two variables; therefore, a change in the volume of the systemic blood flow without concomitant alteration in the volume of the effective pulmonary blood flow cannot influence the percentage oxygen saturation of the mixed venous blood. Under these conditions the percentage oxygen saturation of arterial blood is a function of the mixed venous oxygen saturation (prefixed) and the coefficient of oxygen utilization of the tissues. In predicting the influence of the hæmoglobin value upon the mean systemic capillary oxygen tension a normal systemic blood flow has been presumed because the mean value for the systemic arterio-venous oxygen difference observed in patients investigated (4·34 vols. per 100 ml.) lies very close to the average normal value. The relationship between effective pulmonary flow and percentage oxygen saturation of mixed venous blood at any hæmoglobin level has already been discussed and is obtained from formula 6. The percentage oxygen saturation of arterial blood is obtained from formula 7, and mean systemic capillary oxygen tension calculated from formula 4. Thus mean systemic capillary oxygen tension may be plotted against the effective pulmonary blood flow for any given value of hæmoglobin.

This approach is preferred to that employed by Bing *et al.* (1948), who calculated the gain in tissue oxygen tension due to increased hæmoglobin by subtracting a normal coefficient of oxygen utilization and one modified by the observed hæmoglobin value from the observed percentage oxygen saturation of the arterial blood. The difference between the mean systemic capillary oxygen tensions calculated from these two values of mixed venous saturation was taken to represent the gain (or loss) in oxygen tension directly attributable to the hæmoglobin content of the blood. This method does not recognize that the percentage oxygen saturation of arterial blood is also dependent upon the hæmoglobin level.

Fig. 2 shows the predicted relationship between mean systemic capillary oxygen tension and effective pulmonary flow for hæmoglobin values of 75, 100, 125, 150, 175, and 200 per cent. With a normal hæmoglobin the relationship is approximately linear until the flow has been halved, and thereafter capillary oxygen tension falls with increased rapidity. The position of the other curves demonstrates that increased hæmoglobin produces a substantial gain in capillary oxygen tension when the flow is greatly reduced; thus, with a flow one-quarter of normal, successive equal increments of hæmoglobin from 100 to 125, 150, and 175 per cent will effect a gain in capillary oxygen tension of 7·0, 11·5, and 14·75 mm. Hg respectively. It is theoretically impossible for a patient to exist with a quarter normal effective pulmonary flow when the hæmoglobin is only 75 per cent.

The mean systemic capillary oxygen tension has been calculated in 63 of the patients from the observed percentage oxygen saturation of the arterial and mixed venous blood. Fig. 4 shows these values plotted against the effective pulmonary blood flow for each case with the predicted curve for a normal hæmoglobin superimposed. In 39 patients the effective pulmonary flow was less than half the average normal value and in all but one increased hæmoglobin had produced some gain in mean systemic capillary oxygen tension; this amounted to as much as 16 mm. Hg in one case, and the mean value for the group was 8·3 mm. above that predicted for a normal hæmoglobin. Several of the 24 patients whose effective pulmonary flow was greater than half normal were anæmic and in these capillary oxygen tension was 1·3 mm. below that predicted for a normal hæmoglobin. For the whole series (63) the mean value for capillary oxygen tension was 4·6 mm. Hg above that predicted for a normal hæmoglobin.

These observations lead to the conclusion that increased hæmoglobin plays an important part in maintaining tissue oxygen tension at rest when the effective pulmonary blood flow is reduced to less than half the average normal resting value by a central venous-arterial shunt.

The Exercise Tolerance

Burchell *et al.* (1950) have shown in patients with central venous-arterial shunts that moderate exertion produces a significant reduction of the percentage oxygen saturation of the arterial and mixed venous blood, the extent of the fall during standard exercise varying. Similar observations

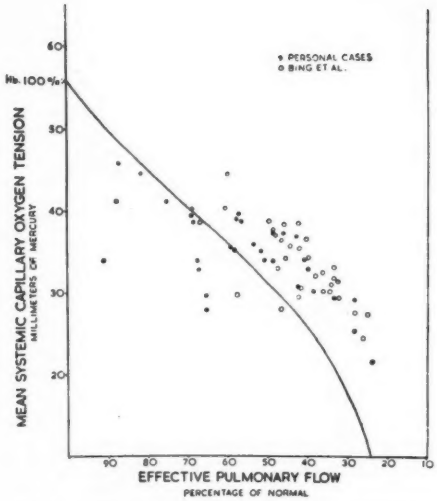

FIG. 4.—The relationship of the mean systemic capillary oxygen tension to the effective pulmonary flow.

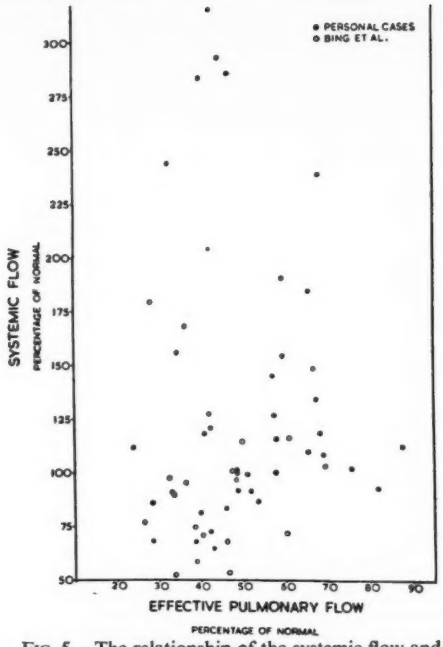

FIG. 5.—The relationship of the systemic flow and the effective pulmonary flow.

have been made on five patients (four with Fallot's tetralogy and one with Eisenmenger's syndrome) who exercised upon a bicycle ergometer during cardiac catheterization; the findings are shown in Table III.

When the effective pulmonary blood flow fails to increase pari passu with the increased oxygen needed for sustained exercise the percentage oxygen saturation of the mixed venous blood must fall, and consequently, mean systemic capillary and tissue oxygen tensions fall.

Although a somewhat artificial procedure, the adaptive value of increased hæmoglobin can be expressed in terms of its capacity to increase oxygen absorption. This is done by determining the difference between the observed oxygen uptake during exercise and the calculated oxygen uptake on the assumption that the hæmoglobin level is normal while the effective pulmonary flow, the arterial and mixed venous oxygen saturations remain at the observed levels. For instance, in Case 15 (Table IV), whose oxygen uptake during exercise was 471 ml., Hb. 27·5 vol. per cent, arterial O_2 47·7 per cent, mixed venous O_2 22·2 per cent, and effective pulmonary blood flow 2·36 l./min., the oxygen uptake at a normal Hb. of 20 vol. per cent is calculated by substituting values in formula 1, and is found to be 344 ml./min. A gain of 127 ml./min. is therefore represented by the observed hæmoglobin content of 27·5 vol. per cent. When this difference is expressed as a percentage of the oxygen absorption calculated for a normal hæmoglobin the figure is of course identical to the observed percentage increase in the hæmoglobin. Therefore, in any given patient with central venous-arterial shunt, the maximum sustainable oxygen consumption (i.e. exercise tolerance) can be regarded as directly proportional to the hæmoglobin content of the blood.

It would appear possible that increased blood viscosity secondary to polycythæmia might modify these conclusions, but we have failed to confirm this in observations upon one patient (Case 18, Table IV). Cardiac catheterization was performed and his response to exercise upon the bicycle ergometer observed. Hæmoglobin was then reduced from 161 to 143 per cent by frequent small

TABLE III

THE EFFECT OF EXERCISE IN FIVE PATIENTS

Case No.	Condition	Oxygen capacity (blood vol. %)	State	Oxygen consumption (ml./min.)	Percentage saturation of blood		Blood flow (litres/min.)		V-A shunt (per centage of systemic flow)
					Arterial	Mixed venous	Systemic	Effec. pulmonary	
15	Fallot	27·5	Rest	176	65	57	8·1	1·7	79
			Exercise	471	48	22	6·7	2·4	65
16	Fallot	24·5	Rest	220	81	53	3·2	2·1	30
			Exercise	675	64	32	8·5	4·3	49
17	Fallot	29·3	Rest	237	79	69	7·8	3·1	61
			Exercise	897	49	34	21·2	5·0	76
24	E. comp.	27·2	Rest	209	88	60	2·8	2·2	21
			Exercise	592	68	26	5·3	3·2	40
18	Fallot	32·3	Rest	285	82	68	6·1	3·3	45
			Exercise	980	73	42	9·9	5·9	41
Ditto after venesection		28·7	Rest	254	78	63	6·0	2·8	53
			Exercise	740	58	35	10·8	4·3	60

TABLE IV

DATA ON ARTERIAL BLOOD COMPOSITION, VENTILATION EQUIVALENT, AND VENTILATION RATIO

(1)	(2)	(3)	(4)	(5)	(6)	(7)
Case No.	Arterial blood			Oxygen ventilation equivalent (VE) (normal=2·78)	Ventilation ratio (VR) VR=VE/2·78	Calculated arterial *p*H
	O_2 capacity (vols. %)	Per cent saturation	Total CO_2 (vols. %)			
8	30·4	81·0	30·4	5·0	1·8	7·31
2 (1)	22·8	81·3	40·9	6·2	2·2	7·35
2 (2)	23·3	77·0	42·3	5·3	1·9	7·39
4 (1)	19·5	71·6	40·8	7·3	2·6	7·40
4 (2)	20·5	88·3	40·2	3·6	1·3	7·38
36 (1)	22·4	79·4	38·7	3·5	1·3	7·38
36 (2)	20·9	86·0	44·2	4·0	1·5	7·37
7 (3)	19·3	76·4	41·8	5·6	2·0	7·40
18 (1)	32·3	82·5	33·0	6·1	2·2	7·30
18 (2)	28·7	78·8	33·7	6·9	2·5	7·31
3	24·6	75·9	40·7	5·0	1·8	7·39
35	18·3	78·4	53·2	5·5	2·0	7·45
10	19·7	87·3	43·9	3·9	1·4	7·36
16	23·6	81·0	38·2	6·4	2·3	7·34
17	29·3	79·1	37·1	4·1	1·5	7·37
5	24·8	79·3	42·3	5·0	1·8	7·37
6	25·8	76·3	36·8	5·0	1·8	7·37
24	27·2	87·7	38·3	4·9	1·8	7·33
19	23·4	79·3	39·3	4·8	1·7	7·37
21	23·7	74·6	36·0	4·3	1·6	7·37
20	16·1	75·1	46·2	3·7	1·3	7·44
25	21·1	89·8	43·7	3·8	1·4	7·36
30	27·9	75·2	36·9	7·5	2·7	7·35
32	26·4	83·8	40·8	6·1	2·2	7·35
Mean S.D.	23·9 ±4·0			5·1 ±1·2	1·9 ±0·4	7·37 ±0·04

venesections; this produced a slight deterioration in his exercise tolerance. Cardiac catheterization was then repeated and demonstrated a significant reduction of the resting arterial and mixed venous oxygen saturations with an increase in the absolute and relative size of the central venous-arterial shunt. His response to the same exercise was again studied; and although he failed to achieve the oxygen uptake observed during the first investigation, the arterial and mixed venous saturations showed greater depression, and the shunt was larger.

Adaptive Value of Increased Cardiac Output

In patients with central venous-arterial shunts the measurements of cardiac output by application of the direct Fick principle presents recognized difficulties. A large collateral circulation to the lungs and left-to-right intracardiac shunts render the effective pulmonary and systemic blood flows erroneously low estimates of the total pulmonary blood flow and left ventricular output respectively. Collateral pulmonary blood flow cannot be measured and therefore an approximate estimate of the size of left-to-right intracardiac shunts—although frequently attempted—is of little value. For this reason variation in the size of the cardiac output as an adaptation to the central venous-arterial shunt can only be considered in relation to the volume of the systemic blood flow.

In the patients observed personally the mean value for the resting systemic arterio-venous oxygen difference ($4{\cdot}34 \pm 0{\cdot}24$ vols per 100 ml.); approximated closely to the predicted mean value for normal subjects in the supine position, and only in patients with pulmonary arterio-venous aneurysms was this consistently reduced ($3{\cdot}39 \pm 0{\cdot}35$ vols. per 100 ml.); therefore an increased systemic blood flow is not a constant accompaniment of central venous-arterial shunt.

The relationship between systemic and effective pulmonary blood flows—calculated from the respective arterio-venous oxygen differences and expressed as percentage of the average normal value—is shown in Fig. 5. Compensatory increase in the systemic blood flow would be shown by a negative correlation between these two values, but none exists. To evaluate the gain from increased resting systemic blood flow it would be necessary to know what effect, if any, this would have upon the volume of the effective pulmonary flow. There is no evidence that an increase of the former produces a proportionate increase of the latter. On the contrary, studies by Hamilton *et al.* (1950) and personal observations upon Cases 6 and 14 suggest that adequate blood flow into the pulmonary artery through a stenosed infundibulum or pulmonary valve is maintained by a high pressure-gradient between the right ventricle and pulmonary artery during systole. When a free communication exists between the two ventricles (as in Fallot's tetralogy) the contents of the right ventricle will be ejected into pulmonary and systemic vascular beds in a proportion that will be determined by the relative resistance offered by each system. A normal systemic peripheral resistance is obligatory if effective pulmonary flow is to be maintained, and relaxation of systemic arteriolar tone will serve only to reduce the pulmonary arterial blood flow in these cases, although it may be accompanied by an increased systemic flow.

The systemic blood flow is the sum of two components: (1) the effective pulmonary blood flow, and (2) the central venous-arterial shunt; therefore, it may be restricted by purely mechanical means if pulmonary stenosis is associated with a septal defect that limits the size of the central venous-arterial shunt. This fact probably accounts for the very low resting systemic blood flow occasionally observed in patients diagnosed as suffering from Fallot's tetralogy and suggests that the aorta does not, in fact, over-ride the ventricular septal defect. The advantage or otherwise of a restricted venous-arterial shunt is difficult to assess because functional capacity depends primarily upon the volume of the effective pulmonary blood flow.

The effect of exercise upon the volume of the systemic and effective pulmonary blood flows has been studied in five patients (Table III). The effective pulmonary flow was increased in all cases; the systemic flow increased in four and fell slightly in one (Case 15; this anomalous finding may have been due to the abnormally high resting flow observed). The contribution of the central

venous-arterial shunt to the volume of the systemic blood flow rose in three and fell in two; in one (Case 18) the response was reversed following moderate venesection.

It has been concluded from these observations that the volume of the systemic blood flow in this group of patients is largely governed by the nature and severity of the cardiac abnormality, and that it cannot, therefore, make any adaptive contribution.

In patients with congenital pulmonary arterio-venous aneurysms the venous blood passes readily into the pulmonary arterial tree and the mean pulmonary arterial pressure is usually normal or sub-normal. The resistance of the normal pulmonary capillary bed is low and will not rise until blood flow is greatly increased, therefore we might expect the relative proportion of venous blood entering the abnormal channels to be little changed by an increase in flow. The ease with which these patients can increase their effective pulmonary blood flow probably accounts for the good exercise tolerance that is usually observed, but there is no evidence to suggest that increased systemic flow is an important adaptive mechanism at rest—in four patients investigated the mean increase of resting systemic flow was approximately 30 per cent above the average normal value.

Respiratory Function

Hyperpnœa at Rest. Table IV presents data on resting ventilation and arterial blood composition from 20 patients with veno-arterial shunt. Four of the patients were re-investigated later when time or treatment had materially altered their clinical status. Thus the table lists 24 sets of observations on 20 patients; showing in Col. 2–4 the results of arterial blood analysis, and in Col. 5–6 the corresponding figures for oxygen ventilation equivalent (VE) and for the ventilatory ratio (VR) derived therefrom. No data has been included from patients in whom the respiratory quotient at rest lay outside the normal limits of 0·7–1·0. The only other exclusions were in cases where the ventilation and the arterial blood data were insufficiently contemporary.

Hyperpnœa—which seems to be the sole abnormality of respiratory function in these patients at rest—could not be assessed in terms of absolute ventilation rates per unit surface area in view of the age-composition of the series. Normal standards exist for adults (Matheson and Gray, 1950; Baldwin *et al.*, 1949), and for males from 11–18 years (Morse *et. al.*, 1949), but not for younger boys or for girls. Instead, therefore, the ventilation equivalent for oxygen (VE) has been employed, since this relates ventilation to oxygen consumption, and therefore is less affected by differences in age and sex. It corresponds to the amount of ventilation (litres, B.T.P.S.) required for an oxygen uptake of 100 ml. (dry, N.T.P.).

The ventilatory ratio (VR) figures (Col. 6, Table IV) are included as required by a later context. The VR represents a useful common notation for different types of ventilatory measurement: it is the ratio any such measurement bears to the appropriate normal standard. The observations of Matheson and Gray (1950) on 100 normal male students provide the normal standard for oxygen ventilation equivalent, their mean value being $2{\cdot}78 \pm 0{\cdot}45$. The VR values of Col. 6 are derived thus: Observed VE/2·78.

Taking twice the standard deviation above the mean as the upper limit of normality, this becomes 3·68 or 1·34 in terms of VR. Only two of the 24 listed observations lie marginally below this limit—both incidentally, from Fallot patients after successful Blalock operations. Thus the very high incidence of hyperpnœa at rest reported by Bing *et al.* (1948) is confirmed in the present series.

As regards the degree of hyperpnœa, comparison with their data is impracticable. Although in their series very high ventilation rates were frequent, in more than half of the records the RQ value at rest was greater than unity, thus making it plain that over-ventilation was at least accessory to hyperpnœa in producing the high ventilation rates observed. The exclusion of such observations from the present series does not guarantee that no over-ventilation occurred, but ensures that the ventilation-ratios recorded cannot have been seriously exaggerated thereby.

Pathogenesis of Resting Hyperpnœa. Bing *et al.* (1949) attributed the hyperpnœa to the prevailing anoxæmia and noted that, since the origin of the latter was extra-pulmonary the hyperpnœic response could have no adaptive value. However, the simple cause and effect relationship postulated is difficult to accept; for the correlation between anoxæmia and hyperpnœa is slight in their data as in our own.

This suggests two possibilities; either that individuals vary surprisingly in their capacity to respond to anoxæmia or that the ventilatory demands thus set up are subject to modification by other influences, themselves independent of the degree of anoxæmia. The latter concept corresponds in essentials with that

of Gray's multiple factor theory (1946, 1950) which visualizes the ventilation ratio during anoxæmia as depending not on the anoxic stimulus alone, but also on the degree to which this is reinforced or inhibited by the levels of arterial *p*H and pCO_2 then prevailing.

Gray's " chemical ventilation equation " (which cannot be reproduced in the space available) defines the quantitative relations between ventilation ratio (VR) and arterial pO_2, pCO_2, and *p*H in normal subjects at rest, over a wide range of induced changes in the latter factors, including all degrees of anoxia compatible with normal neural function. The equation would be a fallible touchstone for the recognition of aberrations of respiratory control in cases of anoxæmia generally, since these mostly lack the normal ventilatory capacity presupposed by the formula. Patients with a veno-arterial shunt, however, are not defective in this respect and failure of the equation to hold good in them might reasonably indicate disturbed central respiratory control.

The data in Col. 2–6, Table IV, was accordingly reviewed with this in mind. Only the briefest outline can be given of the treatment to which it was subjected. Since arterial *p*H values were not known, it was impossible to settle the question by the direct comparison of observed VR with VR as predicted by the equation. Instead, for each set of data the equation was solved for *p*H, using the observed VR as a known term: in other words the theoretical *p*H level was calculated that would give to the sum of the three humoral stimuli the value of the observed VR.

Col. 7 lists the calculated *p*H values. All are within the range 7·30–7·45, which agrees with the range of values determined in their cases by Bing *et al.* (1949). The table exhibits obvious negative correlation between O_2 capacity and calculated *p*H, which is significant in the statistical sense ($r=-0{\cdot}841$, i.e. over 4 times the value of its S.E. of 0·208), but may simply be an artificial consequence of some systematic error in the calculations linked to O_2 capacity. But the regression equation

$$p\mathrm{H}=-0{\cdot}0074(\mathrm{O_2\ capacity}-23{\cdot}87)+7{\cdot}37$$

gives for blood of normal O_2 capacity (20 vols. %) a *p*H of 7·40, i.e. the accepted mean normal value.

A better idea of the significance of this result can be given by saying that, for the mean of the calculated *p*H figures (corrected for O_2 capacity) to be lessened from 7·40 to 7·35 would have required, on the average, thrice the degree of hyperpnœa actually observed: and for its displacement to 7·45, the average ventilation would have had to be slightly subnormal.

These results therefore support the assumption that the level of ventilation in these cases is determined by the normal humoral stimuli, operating at levels conditioned by the circulatory defect. There is no need to invoke any hypothetical alteration of sensitivity of the respiratory centre.

Respiratory Response to Exercise

Patients with a veno-arterial shunt exhibit, in their ventilatory response to exercise, a fundamental abnormality that seems to have escaped comment, although it is as frequent, and in its way as striking as the resting hyperpnœa which has been thoroughly discussed. Part of that discussion, as has been noted, concerned the difficulty in justifying the resting hyperpnœa in terms of useful effect; which makes more curious the failure to remark how frequently the ventilatory response to exercise is defective; for it is in this deficiency's existence that the most obvious justification for the resting hyperpnœa is found. The defect amounts to a retardation—often very considerable—of the normal increase in ventilation upon starting exercise, so that during the first three or four minutes of steady exercise ventilation lags abnormally behind metabolic needs, and only reaches a final plateau after an interval much longer than in normal subjects.

Most of the evidence to be presented on this point is in the results of the standard one-minute, thirty-step exercise of Baldwin *et al.* (1949), which was used throughout the series. When interest was aroused in the nature of the defective ventilatory response, a more informative procedure was adopted, and this will be described first, although only four of the later patients were subjected to it.

Sustained Exercise. Three normal subjects and four of the Fallot patients carried out (after earlier practice), in the supine position, exercise on the bicycle ergometer, sustained at a uniform

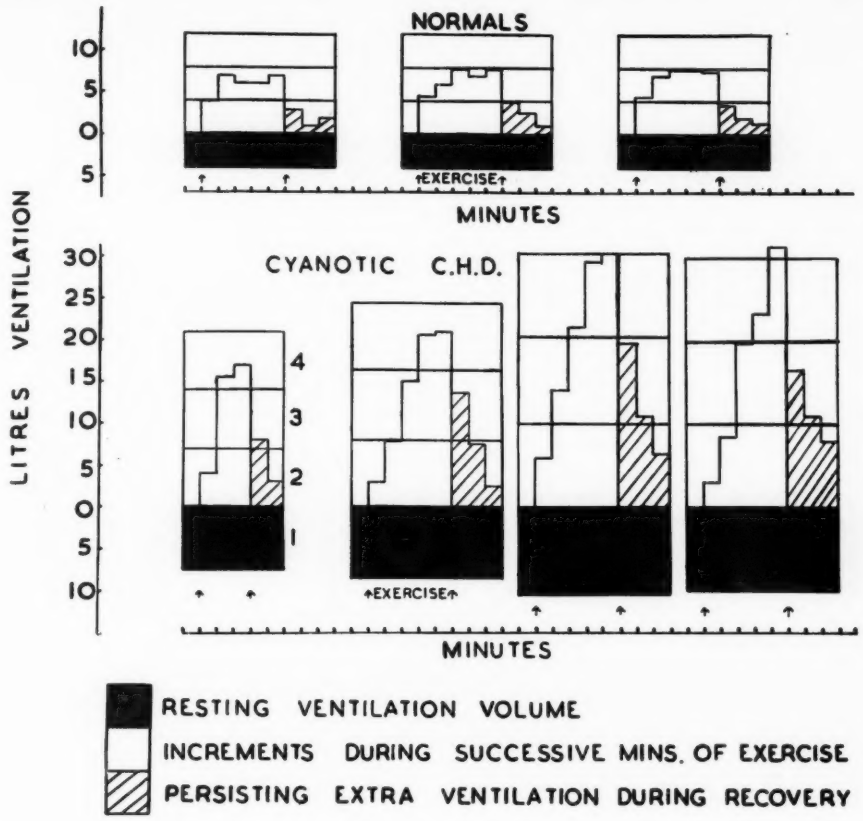

FIG. 6.—The increase of ventilation during and after exercise in normals and cyanotic congenital heart disease.

rate for five minutes and of intensity corresponding to an oxygen uptake per square metre of from 500 to 600 ml. a minute. The procedure has been described, the only difference here being the omission of all sample-taking to preserve continuity of the ventilatory record. The Tissot tracing was uninterrupted through rest, the five minutes for which exercise had to be sustained for the Fallot patients to achieve steady levels of ventilation, and two or three minutes of recovery.

Fig. 6 illustrates the results, showing for the seven subjects block diagrams of the actual ventilation per square metre in each successive minute; with resting ventilation below the line in black, and above it the increases attributable to the exercise; unshaded, during the exercise; and hatched, during recovery. The difference between the responses in controls and in patients is too apparent to require detailed comment. Each normal had achieved 95 per cent of his augmentation of ventilation within ninety seconds of beginning work, whereas none of the patients was comparably near equilibrium even after twice that period. The maximum separation of the groups occurs, however, in the first minute of work when the controls' response exceeds that of the patients most conspicuously as regards the ratio exercise:resting ventilation, but also in the absolute volume of extra ventilation.

This lag of ventilation response must certainly have caused considerable retention of carbon dioxide in the early minutes; and it is obvious that oxygen uptake from the lungs would also have been greatly impaired had not the patients carried over into exercise, as a legacy from their resting hyperpnœa, abnormally high alveolar oxygen tensions. Consequently, abnormally great reductions in these tensions could occur without serious unsaturation developing in the pulmonary venous blood. This effect of the hyperpnœa at rest must constitute a useful protection; for although these patients do eventually stabilize their ventilation—presumably at the level of requirement—the process occupies nearly five minutes during very mild exercise; and without the pre-existing " store " of oxygen in the lungs even this level of exertion would have been difficult to sutain for that time.

Standard One-minute Step Exercise. The results of the standard 30-step exercise are listed in Table V. Its one-minute duration, and the easy nature of the exercise make this a test which nearly every ambulant patient can accomplish; but its brevity means that what is being tested is not respiratory performance under working conditions so much as the efficiency and speed of cardio-respiratory response during the transition from the resting state. Even healthy subjects hardly reach their new equilibrium within the minute period and the slight fall in R.Q. which is normally

TABLE V

RELATION OF ANOXIC PARTIAL VENTILATORY STIMULUS (VRO_2) AND SPEED OF VENTILATORY RESPONSE TO EXERCISE (30-STEP TEST)

(1)	(2)	(3)	(4)	(5)	(6)	(7)
Case No.	Resting arterial pO_2 (mm. Hg)	Corresponding $VRO_2 \times 4{\cdot}02$ (litres/M^2/min.)	Ratio exercise: resting			Ventilation increment in one minute exercise (litres/M^2)
			O_2 uptake	CO_2 output	Ventilation	
4 (1)	38·4	15·2	1·9	1·6	1·5	4·9
21	40·5	12·9	1·9	1·6	1·5	3·1
20	40·9	12·5	1·8	1·8	1·9	4·2
30	41·1	12·3	1·7	1·8	1·7	8·5
3	41·8	11·7	2·1	1·7	2·1	7·9
7 (2)	42·3	11·2	2·1	1·8	1·8	6·5
6	42·3	11·2	1·9	2·1	1·7	5·0
2 (2)	42·7	10·9	2·3	2·1	1·7	5·6
35	44·0	9·8	2·5	2·1	2·2	7·4
7 (1)	45·1	9·0	2·4	2·3	1·7	7·5
19	45·1	9·0	1·9	1·9	2·0	7·0
5	45·2	8·9	2·3	2·4	2·3	8·2
36 (1)	45·3	8·8	2·4	2·3	2·4	8·9
2 (1)	47·8	7·1	2·1	2·7	2·7	15·2
32	50·0	5·9	2·7	2·6	2·1	10·6
36 (2)	53·0	4·4	2·4	2·9	3·3	13·8
4 (2)	57·7	2·8	3·4	3·4	3·3	12·4
25	58·5	2·6	3·3	3·4	3·3	13·4
Mean	45·7	9·2	2·3	2·2	2·2	8·4
± S.D.	±5·8	±3·4	±0·4	±0·5	±0·6	±3·4
Coefficient of correlation (r) with ($VRO_2 \times 4{\cdot}02$)	—	—	−0·83	−0·89	−0·90	−0·85

Arterial pO_2 figures (Col. 2) are for assumed pH of 7·40. In col. 3 ($4{\cdot}02 \times VRO_2$) the ventilatory stimulation (as litres/M^2/min.) corresponding to each pO_2 figure is shown. Cols. 4, 5, and 6 show exercise: resting ratios of gas exchange and ventilation. Col. 7 lists actual increments (over resting levels) of ventilation during the test.

seen indicates that the ventilatory response lags behind the increase in lung blood flow. In all six age and sex groups in Baldwin *et al.'s* (1949) series of normals, ventilation was higher in the first minute after the exercise than during the minute of its performance. Taking their young adult male and female groups together, the mean responses were as follows: (1) ratio exercise: resting ventilation=3·13; (2) ratio exercise: resting O_2 uptake=3·56; and (3) actual increase in ventilation=6·6 (litres/M^2). They give no details of CO_2 output, but it is normal for the R.Q. to fall during the exercise, therefore the exercise: resting CO_2 output ratio should be intermediate between ratios 1 and 2.

Properly carried out (as it was by all these patients) the exercise involves an amount of work that is a direct function of body weight or, practically speaking, of surface area: therefore its cost in extra gas exchange per unit surface area ought to be fairly constant; and if from inadequacy of either the ventilatory or the circulatory responses figures of the order quoted above are not achieved, it is likely that, by the end of the exercise, the degree of CO_2 retention, and probably also of oxygen debt, will be abnormally high.

Results. Table V includes data on the results of the standard step exercise (18 observations on 14 patients; the double data again being from patients whose clinical state had undergone material change between the tests). In contrast to the case of the resting hyperpnœa, there seemed, in the results of the exercise test, to be a rough parallelism between the clinical disability and the defect of ventilatory response to exercise. Moreover, when the latter was plotted against resting arterial oxygen tension (assuming *p*H of 7·40) a non-linear relationship was suggested with the smallest responses to exercise occurring with the lowest arterial oxygen tensions at rest (Col. 2). A much clearer relationship emerged when the oxygen tensions were translated into the corresponding anoxic stimulus (VRO_2) by Gray's formula:

$$VRO_2 = 2{\cdot}118 \times 10^{-8}(104 - pO_2)^{4{\cdot}9}$$

or alternatively (as in Col. 3) into terms of the ventilatory volume equivalent to such anoxic stimulus, by multiplying the above expression by 4·02. (The latter figure was taken from Matheson and Gray's (1950) paper already quoted, as representing normal ventilation volume per square metre or unit VR.)

Table V shows the values of the coefficients of correlation between each set of exercise-responses and the corresponding value of (4·02 VRO_2) in Col. 3. All correlations were negative and more than three times their standard error of 0·242.

Significance of Defective Response. The presence of a veno-arterial shunt might logically be expected rather to enhance than to impair the ventilatory response to exertion; for exertion at once increases the volume of blood shunted to the arterial side, both absolutely and in relation to the total flow, and this effect is greatest in those with conditions (such as pulmonary stenosis or high pulmonary resistance) that commonly produce the lowest arterial saturation at rest. This should result in the early arrival at the respiratory centre and chemo-receptors of much additional humoral stimulation, so that a greater and more immediate ventilatory increase might be expected.

The reason why logical expectation should thus be reversed in the event must for proof await further investigation. But there is one speculative explanation that is hard to resist. Anoxia is known to be a respiratory stimulus only within certain limits, beyond which depression overtakes or succeeds stimulation. The precise level at which this occurs is variable, but Gray puts it at about 30 mm. Hg arterial pO_2, and specifically limits the application of his equation to the range above this. This tension (at a *p*H of 7·40) would correspond to 59 to 60 per cent arterial saturation. No patient listed in Table V had a resting arterial saturation below 70 per cent, but the enlargement of the shunt on exertion must in many have depressed arterial saturation below the critical level before the end of the test—after periods probably determined largely by the arterial saturations before work began.

In thus thinking of a " critical level " of anoxia, it is possible to visualize it either as one at which the ventilatory stimulus has its maximal effect, or, alternatively, as the level at which the effects of still-increasing peripheral chemo-receptor stimulation may be overtaken by those of central depression. In either possibility, the concept illustrated in Fig. 7 is appropriate.

In this figure, similar distances along ordinate or abscissa represent similar ventilation volumes—on

the former the increases (litres/M²/min.) observed during the standard exercise, and on the latter the ventilation (litres/M²/min.) that would result from the anoxic stimulus (VRO_2) existing at rest if it were unopposed by the other partial factors. The three scales provided on the abscissa represent, in downward order: (1) resting arterial pO_2; (2) equivalent VRO_2; and (3) corresponding ventilatory volume. The main purpose of Fig. 7, however, is to illustrate the degree of further anoxic stimulation possible at any level of resting pO_2 before anoxia ceases to stimulate or even becomes depressant to the respiratory centre. To

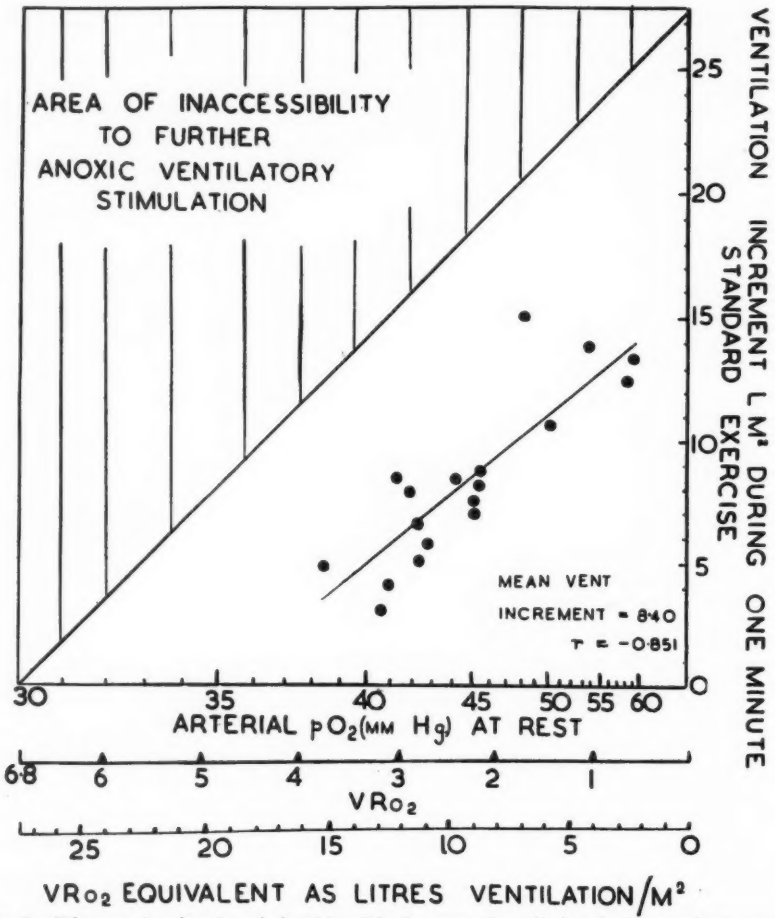

FIG. 7.—Diagram showing the relationship of the increase of ventilation during standard exercise and the arterial pO_2 at rest.

this end, the ordinate has been given a finite length equal to that of the abscissa (which covers the whole range of possible anoxic stimulus-intensity). The square thus formed is divided by a diagonal. The vertical interval between this diagonal and the point on the abscissa corresponding to any resting arterial oxygen tension, represents the effective remaining capacity for ventilatory response to an increase in anoxia, in terms of the volume of additional ventilation such stimulus should evoke. If two patients are imagined with arterial tensions of 35 and 55 mm. Hg respectively, although their actual resting rates of ventilation might well be identical, yet—it can be seen from the diagram—the maximum ventilatory response to further anoxia which could be expected from one would be 8 litres, but from the other 24, before the point of commencing central depression was reached.

However theoretical may be the credentials of the diagonal that divides Fig. 7, and however oversimplified the foregoing example, the plotted increases of ventilation do run to an interesting degree parallel with the diagonal. The regression line is of slightly lesser inclination; but this in any case is inevitable, since at the higher levels of arterial oxygen tension the standard exercise does not call for such increases in ventilation as a stricter parallelism would require.

It is necessary, finally, to anticipate an obvious objection to the suggested role of severe anoxia in retarding the ventilatory responses. Even on evidence from our own supine-exercise tests with concurrent arterial sampling, it may be argued that after initial delay, adequate ventilation rates are ultimately achieved by these patients, in the face of anoxæmia by then more profound than during the initial retarded phase. To this it can only be answered that the hyperpnœa of exercise is known to involve mechanisms additional to those controlling ventilation at rest; and it is easily conceivable that the initial anoxic depression of the centre may be temporary or that it may be overcome when the humoral factors are sufficiently supplemented by whatever specific stimulus the exercise itself affords.

Summary

The cardio-respiratory function of 32 patients with cyanotic congenital heart disease and 4 with pulmonary arterio-venous aneurysms was studied by cardiac catheterization and expired air collection, and the findings analysed to evaluate the mechanisms of adaptation to a central venous arterial shunt.

Resting oxygen uptake lay within the normal range predicted for the sex, age, and surface area of each patient.

A significant negative correlation existed between the hæmoglobin concentration and the resting effective pulmonary blood flow when the latter was expressed as the reciprocal of its arterio-venous oxygen difference. Analysis of the findings in 36 patients with the tetralogy of Fallot published by other workers confirmed this relationship.

Increased hæmoglobin concentration plays an important part in maintaining tissue oxygen tension at rest when the effective pulmonary blood flow is reduced to less than half normal because it enables oxygen uptake to be maintained without profound depression of the oxygen saturation and tension of the venous blood. During exercise of any given patient with a central venous-arterial shunt the maximum sustainable oxygen consumption can be regarded as directly proportional to the hæmoglobin content of the blood.

Increase in systemic blood flow is valueless as an adaptive mechanism unless accompanied by increase in effective pulmonary blood flow. Resting systemic flow varied widely from case to case, but the mean value for the group, expressed as the reciprocal of its arterio-venous oxygen difference, was normal.

The circulatory response to sustained exercise was studied in five patients. The effective pulmonary blood flow increased in all; the proportion of venous blood entering the lungs fell in three patients and rose in two. There was no apparent relationship between the findings at rest and the hæmodynamic response to effort.

Moderate or considerable resting hyperpnœa was present in all patients except a small minority in whom anoxæmia was either minimal or extreme. It was unrelated in its degree to any other single index of disability; but if arterial blood composition was considered as a whole and CO_2 as well as O_2 taken into account, a relationship became obvious. Gray's multiple-factor theory of respiratory control seemed to have the same validity of application to these patients as to normal subjects.

The respiratory response was studied during two forms of exercise. A standard one-minute step-exercise was performed by most of the patients. Observations were made on a smaller number of patients and normal subjects during exercise sustained until ventilation stabilized: this took at least twice as long for the patients as for the controls. The results of the one-minute exercise also revealed a delayed respiratory response. This seemed to be directly related to the severity of resting arterial anoxæmia. The relationship was linear if the resting anoxæmia was converted (by Gray's equation) into terms of " anoxic partial stimulus."

Resting hyperpnœa, it is suggested, may in part constitute an insurance against the contingency of exercise; maintaining reserves of oxygen in the alveolar air, which can be consumed in the first minute or two of exercise before ventilation becomes adequate.

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PHÆOCHROMOCYTOMA

BY

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The successful diagnosis and removal of phæochromocytomata have been reported with increasing frequency during the past few years, and it is probable that many cases have been missed in the past. At this hospital, six tumours have been removed since 1948, while none was recognized either at operation or post mortem during the preceding twenty years.

This paper is based on five cases, three of them not previously described and two reported by Barnett *et al.* (1950). It is concerned especially with the clinical diagnosis and its confirmation by such methods as the biological assay of adrenaline and noradrenaline in the urine, the use of so-called adrenolytic drugs, and the estimation of skin blood flow. We also report assays of the urine and of the tumours in two cases not under our care.

Case Reports

Case 1. W.H., a man, aged 38, was well until 1946, when he developed increasing lassitude and anorexia and was found to have a B.P. of 180/110. Subsequently, he developed attacks of pallor, sweating, "goose-flesh," vomiting, and breathlessness. He was admitted to Chase Farm Hospital on 20/7/48 in a particularly severe attack, and was diagnosed as having a phæochromocytoma by Dr. T. Simpson. There was profuse sweating and pallor, a B.P. of 200/140, bilateral papillœdema with retinal exudates and hæmorrhages, cardiac enlargement, pulsus alternans, gallop rhythm, and a mass palpable in the right loin.

A phæochromocytoma was removed at St. Mary's Hospital on 23/9/48; he has remained symptom-free since with resolution of the retinal changes, but the blood pressure which was 160/120 until 10 months after the operation had risen to 230/130 four years afterwards.

Case 2. B.H., a man, aged 31, had attacks of pallor and bradycardia as a boy of eleven which had led to the discovery of a left bundle branch block with short P–R interval (Case 7 of Wolff, Parkinson, and White, 1930). These attacks subsided, but at the age of twenty-three he began to get attacks of epigastric discomfort, followed by slow, forceful palpitation, pallor, and sometimes throbbing headache, nausea, vomiting, and dyspnœa. His blood pressure between attacks varied from 120/86 to 170/110 and always rose during attacks, the highest recorded being 254/154. They were also marked by sweating, shivering, and slight bradycardia.

A phæochromocytoma was removed on 12/11/49. He has been symptom-free since, his blood pressure on 6/6/52 being 135/80.

Case 3. M.J., a women, aged 66, who had attacks of palpitation for 2 years, was admitted to hospital after three attacks of severe dyspnœa with copious expectoration, sweating, and vomiting. The skin was found to be pale, cold, and sweating; the blood pressure varied from 150/90 to 270/180; marked enlargement of the left ventricle was present, with a presystolic gallop rhythm, and there were retinal hæmorrhages and soft white exudates, but no papillœdema. Rises in the very labile blood pressure were associated with increased pallor, sweating, vomiting and usually tachycardia, but no sharply defined paroxysms were observed.

Removal of a phæochromocytoma from above the right kidney on 30/10/51 was followed by a disappearance of all symptoms. Eleven months later the blood pressure was 165/100.

Case 4. E.G., a women, aged 40, with neurofibromatosis, was admitted to hospital having had attacks

of palpitation for 5 years accompanied by headache, dyspnœa, sweating, and often preceded by vomiting. She had been increasingly breathless on exertion for 9 months. The systolic pressure between attacks varied from 230 to 200 mm. Hg and the diastolic from 150 to 120 mm. Hg. Attacks, lasting 5–10 minutes, of extreme pallor, sweating, dyspnœa, and tachycardia were accompanied by a rise of pressure to over 300/200 mm. There was presystolic gallop rhythm but no cardiac enlargement. Papillœdema, retinal hæmorrhages, and exudates were present.

Removal of a phæochromocytoma on 10/12/51 was followed by a disappearance of symptoms and a gradual regression of the retinal changes, but the blood pressure, after a temporary fall, was 240/140 seven weeks after the operation.

Case 5. D.K., aged 33, recently qualified as a doctor, had been troubled for 4 weeks by attacks in which he developed a sense of constriction in the throat, regular, forceful, but not rapid palpitation, and a throbbing frontal headache with occasional vomiting. He and his friends observed a swelling in the neck during the attacks which they attributed to enlargement of the thyroid gland. Blood pressure varied from 120/60 to 140/80 between attacks and rose to a maximum of 214 mm. Hg systolic and 105 diastolic during attacks, which were accompanied by slight pallor, sweating, and bradycardia, and by an increase of 3–5 cm. in the neck circumference due to swelling of the thyroid gland.

A phæochromocytoma was removed on 20/12/51. He has been symptom-free since and his blood pressure was 120/65 nine months later.

The urinary excretion and tumour content of pressor amines was also estimated in two other cases not seen by us who had phæochromocytomata successfully removed. These results are given in Tables III and IV under Case F (by kind permission of Dr. F. T. G. Prunty of St. Thomas's Hospital, London) and Case G (by kind permission of Dr. C. M. Seward and Dr. G. M. Colson of the Royal Devon and Exeter Hospital).

Diagnosis

Although reliance on pharmacological tests to confirm the diagnosis of phæochromocytomata is likely to increase, the recognition of certain combinations of symptoms will always be essential in suggesting the possibility of the condition. The majority of these symptoms have been adequately described (Mackeith, 1944; Smithwick *et al.*, 1950) and need only brief mention here.

All our patients had symptoms that should suggest the diagnosis. Attacks of palpitation were a prominent feature in four of them and were always remarkable for their forcefulness; in two (3 and 4) they were rapid, and in two (2 and 5) slow. We would emphasize that palpitation, associated with bradycardia, is a fairly common feature of this condition. The ratio of excreted noradrenaline to adrenaline was high in Cases 3 and 4, who showed tachycardia, whereas it was relatively low in Case 5, who had bradycardia in his attacks. High noradrenaline output should therefore not necessarily be inferred in patients with this lesion who show bradycardia, despite the findings of Barcroft, Konzett, and Swan (1951), who usually noted bradycardia during infusions of small amounts of noradrenaline. One of us (W.S.P.) has observed tachycardia during infusions of larger quantities of noradrenaline in two patients.

The onset of palpitation was not always clearly defined. It usually lasted 5–15 minutes, but might last several hours. In all, the attacks ended by gradual reduction in the vigour of the pulsations, and tachycardia, if present, subsided gradually. Severe and throbbing headache sometimes occurred with the palpitation, and was often associated with vomiting. Pallor, sweating, and some degree of breathlessness during the more severe attacks were usually noticed by the patients. " Goose-flesh " (Cases 1 and 5) and retrosternal pain (Cases 2 and 4) were each reported by two patients, and the attacks occurred at night in four (Cases 2, 3, 4, and 5). Sensations of fear were volunteered by only one (Case 1).

The appearance of the patients during an attack was striking. Beads of sweat were usually visible on a uniformly pale skin, which was cold to the touch, and the forcibly beating heart shook the whole chest. The observation by relatives and friends of such objective changes during an attack may be helpful since the symptoms are often thought to be due to a nervous tachycardia. The wife of one patient (Case 2) strongly rebutted such a diagnosis on the grounds that she was often wakened before her husband by the shaking of the bed during his attacks at night.

The hypertension in two cases (2 and 5) was intermittent with normal pressure between attacks. In the other three (1, 3, and 4) the pressure never fell to normal levels, but the term "chronic (or sustained) hypertension" (Green, 1946; Swan, 1951) seems inappropriate in view of the marked variability of the pressures. Although from time to time cases of phæochromocytoma are reported with little variation in the blood pressure (Lumb, 1951), we have not seen a case in which the hypertension showed the degree of stability observed in most patients in hospital with essential hypertension.

Left ventricular failure is a well-recognized danger for such patients, and occurred in Case 3 with typical cardiac asthma. Together with retrosternal pain, it is, perhaps, responsible for the occasional mistaken diagnosis of myocardial infarction in phæochromocytoma.

Certain less-known features observed in our patients deserve mention. In two (Cases 2 and 5) attacks were precipitated by straining at stool; we have been unable to find any previous account of this. One (Case 2) thought attacks were associated with lying on the right side, and precipitation by exertion was noted in Cases 2 and 5, although the attacks were no more severe than those occurring at rest.

Enlargement of the thyroid gland during attacks has been recorded in this condition (Strombeck and Hedberg, 1939; Bauer and Belt, 1947). It was observed previously in this hospital that infusions of noradrenaline repeatedly produced such a swelling in one normal subject (Barnett *et al.*, 1950). No vascular bruit was heard over the thyroid in such incidents in our patient (Case 5), but it would seem likely from the rapid development and subsidence of the swelling that it is due to vascular engorgement. Its occurrence is so distinctive that its value in diagnosis can well be stressed.

Auriculo-ventricular dissociation (ventricular rate 50) was detected in Case 5 during attacks by noting a variation in the intensity of the first heart sound and was confirmed by electrocardiography. It has been described in this condition (Burgess *et al.*, 1936) and reproduced experimentally by noradrenaline infusion by Barnett *et al.* (1950), who attributed it to vagal stimulation in response to the rise of blood pressure.

Neurofibromatosis (Case 4) was found in 9 of the 152 cases reviewed by Mackeith (1944). The association with the Wolff-Parkinson-White syndrome found in Case 2 has not, to our knowledge, been previously reported and is probably fortuitous.

Transient blurring of vision during attacks (Case 2), lasting for a number of hours, is an unusual symptom. We have no evidence as to its cause. It is recorded also by Crowther (1951).

Two of our patients (Cases 1 and 4) had papillœdema and, with one other (Case 3), showed retinal hæmorrhages and soft exudates. Two, and possibly three, therefore, had hypertension in the malignant phase, as judged by the fundi. In all three the renal functions tested were normal; the urine of two (Cases 3 and 4) contained albumin and granular casts, but that of Case 1 showed neither albumin nor casts. Arteriolar fibrinoid necroses were not found in the adrenals of any of our cases, nor in a renal biopsy taken from Case 1. In a review of 50 published cases, Green (1946) was able to find only 4 instances of malignant hypertension, but clinical criteria alone were mentioned for this diagnosis. Platt and Davson (1950) report a case with bilateral phæochromocytomata, whose kidneys showed the "naked eye and microscopic characteristics of malignant nephrosclerosis."

Two patients showed fever and leucocytosis, which are not uncommon in this condition; thus in Case 1 the temperature rose on occasions to 102° F and a blood count showed 14,000 W.B.C. per c.mm. with 62 per cent neutrophil polymorphs; the fever was less marked in Case 3 (99°–100° F), and the blood contained 15,000 W.B.C. per c.mm. with 75 per cent neutrophil polymorphs. We have been unable to correlate these signs with hæmorrhage into the tumour.

The duration of the paroxysms was between 5 and 30 minutes in the cases with intermittent hypertension (2 and 5), as it was in the early stage of Case 1; Case 4 throughout showed paroxysms of a similar length. The attacks in the latter stages of Case 1 were too ill-defined for estimation of their duration; in Case 3 they continued for as long as six hours.

Localization of the Tumour

All five patients in this series had right suprarenal tumours. Evidence as to localization was forthcoming in all except one (Case 4); a palpable mass in the abdomen in Case 1 was confirmed as a suprarenal tumour by perirenal air insufflation; increasing tenderness in the upper abdomen was on the same side as a radiological soft-tissue shadow in Case 5, and a soft-tissue shadow alone in Case 2 was sufficient to lead to the exploration of the correct suprarenal; in Case 3, the low position (both clinically and radiologically) of the kidney was the sole (but correct) indication.

Thus there was direct evidence of a tumour of the suprarenal gland in three cases (1, 2, and 5). In the other two perirenal air insufflation was considered but rejected because of the risks, not only of air embolism (Blackwood, 1951), but also of precipitating severe paroxysms of hypertension (Mackeith, 1944) in patients showing left ventricular failure and malignant hypertension. In view of the high proportion of right-sided tumours in reported cases (Strombeck and Hedberg, 1939; Smithwick *et al.*, 1950), the safest procedure in these two was considered to be exploration of, first, the right suprarenal and then, if necessary, the left. In both instances the tumour was found at the first operation.

Localization by unilateral abdominal compression, with the induction of a paroxysm thereby, was not successful in our patients.

Special Diagnostic Procedures

Maximal Heat Elimination from the Hand. The heat elimination from the hand, made maximal by rapidly heating the body, is a measure of the rate of blood flow through the hand after release of vasomotor tone from its vessels (Pickering, 1936). It was measured by following the temperature changes of water in a calorimeter in which the hand is immersed as described by Barnett *et al.* (1950). In four of the patients it was abnormally low, but in Case 5 it was normal (Table I). Two of the patients had hypertensive attacks during this test, with a further fall in heat elimination (Cases 2 and 4). Following operation the maximal heat elimination rose to the normal level (above 60 calories per 100 ml. of hand per min.) even in the patients in whom hypertension persisted (Cases 1 and 4).

TABLE I
Maximal Heat Elimination

Case	Calories per 100 ml. of hand per min.		B.P. during test, mm. Hg	
	Before operation	After operation	Before operation	After operation
1 W.H.	35	90	160/115	200/140
2 B.H.	24	76	130/90	122/82
3 M.J.	37	80	220/120	180/85
4 E.G.	34	86	190/140	150/90
5 D.K.	93	116	130/86	116/74

The low values for heat elimination obtained before operation in all our patients, except Case 5, support the view that circulating vasoconstrictors are usually present in this condition, particularly since the values rose to normal after operation. There is not necessarily a raised blood pressure at the time of a test which gives a low value, perhaps indicating that the circulating amines are sufficient to constrict the skin vessels without causing a general rise of blood pressure. The maintenance of normal pressures may be due to dilator reflexes, which do not affect the skin vessels. It is not known whether it is possible to infuse noradrenaline or adrenaline at a rate sufficient to constrict the hand blood vessels without causing a rise of blood pressure. The precipitous fall in blood pressure, which occurs in most patients immediately after the tumour is removed, suggests that depressor mechanisms have been called into play by the circulating pressor amines, but there is as yet no evidence as to whether the depressor mechanisms are humoral or nervous.

Blacket *et al.* (1950) observed a similar fall in rabbits' blood pressure after stopping infusions of noradrenaline, and suggested a humoral mechanism on indirect evidence.

Case 5 had a normal heat elimination, even during a minor attack. This test is therefore fallible, but remains a simple and useful one.

Pharmacological Diagnosis. Some of these methods of diagnosis have recently been reviewed (Entwisle *et al.*, 1951; Evans *et al.*, 1951), and consist in the use of so-called antagonistic drugs, like piperoxane (Goldenberg *et al.*, 1947), or " stimulating drugs," which precipitate typical hypertensive attacks, like histamine (Roth and Kvale, 1945). Our procedure in using the antagonistic drugs was to set up an intravenous infusion of saline and to inject the drugs into the tubing. The effect of a control saline injection was compared with that of the antagonistic drug. A maximum of 20 mg. of piperoxane was given in one minute; sometimes headache, nausea, or substernal or abdominal pain stopped the injection. The results of such injections are shown in Table II.

TABLE II

THE EFFECTS OF INFUSIONS OF PIPEROXANE

Case	Dose (mg.)	B.P. mm. Hg	
		Before injection (mean)	After injection (maximal effect)
1 W.H.	15	185/125	225/130
3 M.J.	20	200/120	170/70
4 E.G.	8	224/140	250/160

Experience here with piperoxane has been discouraging, since the test was negative in Cases 1 and 4, though positive in Case 3. Goldenberg and Aranow (1950) suggest that the negative results in proven cases may be due to a secondary hypertension. This is supported by the persistence of the hypertension after removal of the tumours in these two cases. False negative results have been reported by Tulloh (1952) and false positives in uræmic hypertensives (Emlett *et al.*, 1951). The side effects of this drug are frequently unpleasant, and the use of " regitin " (C7337) has been recommended, since it is said to give a more definite and prolonged fall in pressure, with few side effects (Emlett *et al.*, 1951). It was injected in a dose of 0·08 mg. per Kg. during one minute. In Case 3 it was used before operation for diagnosis, the pressure falling from 230/130 to 160/70 within three minutes. The effect, although less, was still present two hours after injection, when the pressure was 190/105. It was also used in Case 4 to control the rapid rise of pressure during operation, and caused a fall from 260/160 to 170/105 within one minute.

These drugs are, of course, useless for diagnosis in cases where the blood pressure is usually normal and only raised for short episodes. The use of drugs like histamine, which precipitate attacks, is clearly to be avoided if possible, as they may not be without risk, and both false negative and positive results have been reported (Evans *et al.*, 1951). They were not used in these cases.

Pressor Substances in Blood, Urine, and Tumour. The original observation that an adrenaline-like substance was present in the blood of a patient with this condition was made by Beer *et al.* (1937). Owing to the low concentrations usually present and the non-specificity of many methods, this assay is difficult by any means. A firm basis for the diagnosis was claimed by Engel and Euler (1950) by estimation of the daily urinary excretion of adrenaline and noradrenaline. They reported cases where the excretion was greatly raised, and further reports appeared by Euler (1951) and Goldenberg (1951). These findings have been confirmed (Table III).

Method—Urines. The method of estimation used here was based on that of Euler and Hellner (1951). The urine was not hydrolysed with HCl, so that only the free amine in the urine was estimated. The amines were extracted from part of a 24-hour specimen by selective adsorption on alumina. They were assayed biologically using the blood pressure response (Hg manometer) of the anæsthetized rat (nembutal 4–5 mg.

per 100 g. intraperitoneally). The total pressor amines were estimated by matching with known solutions of adrenaline and noradrenaline. The ratio of noradrenaline to adrenaline in the mixture was measured by using dihydroergotamine which reverses the action of adrenaline, but merely reduces the pressor action of noradrenaline. A mixture of the amines then gives a biphasic response with an initial fall due to adrenaline, followed by a rise due to noradrenaline. The response given by the urine extract was matched with the appropriate mixture of noradrenaline and adrenaline.

TABLE III

TOTAL 24-HOUR URINARY EXCRETION OF PRESSOR AMINES (μG.)

Case	Before operation		After operation (total)
	Total	Ratio (noradrenaline/adrenaline)	
3	4375	3·0	40
4	500	4·0	70
5	412	1·5	45
F	1082	9·0	25
G	600*	0·5	—

* Urine collected for 14 hours only.

The maximum daily excretion found here in 28 patients with hypertension not due to phæochromocytomata was 70 μg. noradrenaline and adrenaline as the free amines. The daily excretion in the proved cases here reported was always more than five times this value. As might be expected, the excretion in phæochromocytomata is partly paroxysmal; thus in Case 4, 100 ml. of urine collected in the hour following a severe attack contained 500 μg. of pressor amine, as compared with the same amount excreted during 24 hours when only slight attacks were experienced. The case which best demonstrates the value of the urinary assay is Case 5, who had only three attacks of 5 minutes duration in one 24-hour period, yet excreted six times the normal amount. The amine release from the tumours, while partly paroxysmal, is probably continuous in some cases, as is suggested by the low maximal heat eliminations discussed previously. Patients with great differences in the severity of their symptoms and signs may have, on occasion, the same level of urinary excretion. Case 4, with severe attacks, had a similar 24-hour urinary excretion to Case 5, with slight attacks (Table III). The level of excretion is directly related, however, to the severity of the attacks during the period of urine collection, and a patient with severe, frequent attacks always had a higher excretion than one with mild, intermittent attacks (see discussion of Case 4, previously). There is therefore no evidence that individual variation in response to the same amount of circulating amine could account for the difference in severity of the symptoms. It has been claimed by Shapiro *et al.* (1951) that a patient with a phæochromocytoma was less sensitive to injected adrenaline than normal subjects. It must be pointed out that it is not known if the level of urinary excretion is directly or uniformly related to the blood level of these amines. Little is known about excretion of large amounts of adrenaline and noradrenaline, but Euler and Luft (1951) found that only 1 per cent of noradrenaline infused in small amounts (10–20 μg. per minute) was excreted in the urine. In Case 3, who had severe attacks and a very high urinary excretion, presumably a much greater percentage of amine was excreted. After operation the excretion returned to normal in all cases, and remained so in Case 4 despite the subsequent rise of blood pressure. The excretion in Case 1 was not measured before operation, but 3½ years after operation, when his blood pressure was 200/140, his excretion was normal.

Excretion in the urine is not the only way in which adrenaline and noradrenaline are removed from the circulation. They also occur in the urine as inactive ethereal sulphates and glucuronides. We have not investigated the possibility of marked individual variation in this mode of inactivation. Oxidation by amine oxidase is another conceivable means of removal (Burn, 1952).

Method—Tumours. Part of the tumour was taken into 10 ml. N/10 HCl per g. of wet tissue and ground up. The rest was used for sections. All showed the typical naked-eye and microscopic features of phæochromocytomata. The amine content of the tumours was assayed by the same method as for urine, though it was found possible to use dilutions of the neutralized crude extracts in the rat without depressor effects.

TABLE IV

PRESSOR AMINE CONTENT OF TUMOURS

Case	Tumour (weight in g.)	Amine content (mg. per g. of wet wt.)	Ratio (noradrenaline/ adrenaline)
3	50	1·6	4·0
4	46	2·0	9·0
5	67	2·4	1·9
F	72	3·2	9·0
G	680	4·7	0·66

There seems to be no correlation between the size of the tumour and its amine content on the one hand and the clinical picture on the other. Case 4 had malignant hypertension with symptoms for five years, while Case 5 had mild symptoms for six months. The size of the tumours and their amine content were similar (Table IV). This may be accounted for by differences in the rate of tumour growth.

The rate of release of amine varies considerably from case to case, and not necessarily in relation to the tumour size and amine content. Case 3 had a urinary excretion 8 to 9 times greater than Case 4, but the tumour size and amine content were nearly the same (Table IV). This raises the question of which factors are important in controlling the release of amine from the tumour. It is not clear if a mechanical stimulus, like palpation or postural change, is directly effective or whether it initiates a nervous reflex. No account of the nerve supply to these tumours has been found. As mentioned above, palpation did not provoke an attack in any of our patients, but in Case 4 two typical attacks were induced by heating during the maximal heat elimination test. This was possibly a nervous reflex, though humoral factors are not excluded.

The relative proportion of amines in the tumours was similar to that in the urine as stated by Engel and Euler (1951). There was no extra-suprarenal tumour in the present series, yet the proportion of noradrenaline in the urine was very high in two of the cases (4 and F, Table III). This opposes the view of Euler (1951) that it is possible to presume an extra-suprarenal site in cases with a high percentage of noradrenaline excretion.

It is clear that the estimation of the urinary adrenaline and noradrenaline offers the best available special method of diagnosis. Certainly no false positive result has been obtained, but it may be premature to claim that no false negative has occurred.

OPERATION AND THE MANAGEMENT OF THE PATIENT

All the tumours were successfully removed by Mr. A. Dickson Wright under general anæsthesia given by Dr. L. H. Morris. In all our patients except one (Case 2) the blood pressure fell after removal of the tumour, and was restored to normal levels by intravenous infusions of noradrenaline or adrenaline in saline. Noradrenaline, which is a more effective pressor agent, was used in the three most recent cases, and it was necessary to infuse a large amount to maintain the pressure. The concentration varied from 10 to 20 mg. noradrenaline per litre of normal saline, and the rate was adjusted according to the effect on blood pressure. The infusion was first slowed and then stopped after 24 to 36 hours. Atropine was never used before operation in these patients as Barnett *et al.* (1950) have shown the increased rise in blood pressure which sometimes accompanies infusions of noradrenaline after administration of atropine.

Course and Prognosis

A feature of considerable interest in this series is the length of history; with this it is convenient also to consider the length of remissions (if any), and the prognosis. Case 1 had symptoms for 18 months; remissions did not exceed a week even in the early stages, and later were absent: with the advent of malignant hypertensive retinopathy and increasingly severe symptoms, the prognosis must have been extremely grave. In Case 2 there is no doubt that attacks had occurred for 8 years before operation, and it is at least possible that they began at about the age of 11 years, 20 years before operation. Remissions lasting several months occurred after 1941, but if his childhood symptoms represent the effects of this tumour, then there was freedom from symptoms for 10 years. Although this would indicate a benign course, he was rapidly deteriorating in health, with increasingly severe and frequent attacks and breathlessness. It is worth noting that his tumour was the largest in our observed cases, weighing 200 g. In Case 3, attacks had occurred for 2 years and were separated by intervals of a week or two at first; latterly her course was one of rapid deterioration, with frank left heart failure. In Case 4 the attacks had been of moderate severity for 5 years, with apparently remissions of not longer than a few days, even at the commencement; her downhill course into malignant hypertension was slow but continuous. Case 5 had the shortest history; the most direct questioning could not elicit symptoms for more than 6 months before operation, and he himself had not been disturbed by symptoms for more than 6 weeks; the attacks were, from the start, not more than a few days apart. Despite this short history, his tumour was the second largest.

All our patients, except Case 2, showed the profound fall in pressure at operation which is usually seen after removal of the tumour. In Case 1 it has risen again to a high level, but the retinal signs of malignant hypertension, which disappeared in the first three months after operation, have not returned; he has been at full-time work for two years. Case 2 has a normal blood pressure, is symptom free and at work. In Case 3 the pressure is near to normal, and she is free from symptoms. Ten months after operation on Case 4, paroxysms have not returned, but the pressure has risen again to high levels; the fundi, however, show improvement, with hardening of the exudates and disappearance of the papillœdema. Case 5 has a normal bood pressure, and is at full-time work, with no symptoms. In three of our patients, therefore, the pressure has remained at or near normal since operation. In the other two, however, there has been a return to high levels of pressure within a few weeks. Both originally showed the retinal signs of malignant hypertension and these disappeared with operation in both and have not returned.

The reason for the persistent hypertension in these two patients after excision of the tumours is unknown. The hypertension was not due to secretion from a second phæochromocytoma as shown by the normal values found for the urinary pressor amines and the return to normal of the maximal heat elimination from the hand. It is possible that both were cases of co-called essential hypertension and that the phæochromocytoma was superimposed. Evidence of an inherited disposition to hypertension was not convincing. The only sister of Case 1 had died from hypertension in childbirth, aged 20, at which age severe essential hypertension is very rare; the pressures of his parents were unknown and his brother, aged 42, had a normal pressure. The mother of Case 4, aged 69, had a blood pressure of 170/105; that of the father, who died of pneumonia, was unknown. The incidence of diastolic pressures of 120 mm. Hg or above, between the ages of 40 and 49 in a random sample of the general population, has been found to be 1·2 per cent in both men and women (personal observation, M.H. and G.S.C.S.). Thus it is extremely unlikely that two out of five cases would have shown pressures of this order if the previous existence of a phæochromocytoma were not significant. Moreover, the only other case observed in this hospital and reported by Barnet *et al.* (1950) also showed persistent hypertension after excision of a phæochromocytoma. We are thus led to the conclusion that the residual hypertension was in some way a consequence of the tumour. This conclusion, which must be provisional, is in line with other experience that hypertension may persist after what may be regarded as its primary cause has been removed.

Thus Pickering and Heptinstall (1953) reported seven cases of presumed unilateral pyelonephritis, three of which experienced no fall of pressure after excision of the diseased kidney, and all of which showed some residual hypertension.

Summary

Five cases of phæochromocytoma are reported and their clinical features discussed.

Special diagnostic procedures are considered—of these the maximal heat elimination is simple and useful. Pharmacological tests with piperoxane, regitin, and histamine are discussed.

The estimation of urinary adrenaline and noradrenaline is confirmed as the best available special method of diagnosis.

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THE ATRIAL ELECTROGRAM IN MITRAL STENOSIS

BY

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The exposure of the heart during the operation of mitral valvotomy has presented the opportunity of obtaining electrograms from the outer surface of the atria of cases of mitral stenosis. Analysis of these tracings has helped to explain the cause of the broad, notched P wave often seen in this condition. Since only a single-channel electrocardiograph was available, the correlation of the various deflections in the two atrial leads with each other and with those from indirect leads was not as accurate as could be wished, but it has been sufficient for certain conclusions to be drawn.

Unipolar leads were used—a pad of cotton wool soaked in saline and attached to a loop of silver wire forming the exploring electrode. Leads were taken from the body of the right atrium and from the body and appendage of the left atrium in positions as similar as possible in each case; though it was not possible to place the electrode so accurately on the right atrium, since its exposure was not so good as that of the left. Records were usually made at the full standardization of a one-centimetre deflection representing one millivolt, but this had sometimes to be reduced a variable amount.

One important technical problem was to prevent distortion of the record by the mechanical effect of the contraction of the heart: this, however, was mainly ventricular and so, coming after the QRS complex, did not distort the earlier, more important deflections. More troublesome were the ectopic arrhythmias that are frequently seen during this operation (Campbell and Reynolds, 1952) and occasionally no record of the sinus rhythm was obtained.

Measurements were made of the height and width of the P waves, and of the P–R interval from the beginning and peak of the major deflection of the P wave to the beginning and peak of the major deflection of the QRS complex. Where positive and negative deflections were approximately equal an average of the two was taken.

These investigations have been carried out in 29 cases of mitral stenosis, but the findings were incomplete in 4 of these due to a distorted record in one and an ectopic pacemaker in three. Similar investigations were made for comparison in 11 cases of congenital heart disease and in 8 of carcinoma of the bronchus.

RESULTS

There was a wide variation in the size and shape of the P waves in the atrial tracings, though this was not as great as the extremes of the ranges might suggest. Table I shows the average of these measurements in the three groups of cases studied; and the relationship in size and time between the two atrial P waves in the three groups is shown diagrammatically in Fig. 1. Representative standard leads and atrial electrograms from eight of the cases of mitral stenosis are illustrated later in Fig. 2 and 3.

The form of the P wave from the right atrium of the cases with mitral stenosis varied from an entirely positive to an entirely negative deflection, and predominantly positive and predominantly negative deflections were present in about equal numbers. From the left atrium a positive

TABLE I

AVERAGE MEASUREMENTS OF THE P WAVES IN THE ATRIAL ELECTROGRAMS IN THE CONTROL CASES, IN MITRAL STENOSIS, AND IN CONGENITAL HEART DISEASE

Group	P waves in atrial electrograms					
	Height (mv.)			Width (sec.)		Asynchronism between those from right and left atria (sec.)
	Right atrium	Left atrium	Left appendage	Right atrium	Left atrium	
Controls	0·7	1·0	1·6	0·077	0·071	0·028
Mitral stenosis	1·2	2·0	2·2	0·086	0·078	0·051
Congenital heart disease	2·2	1·3	—	0·083	0·060	0·033

deflection was usually equal to or greater than the negative one, and from the left appendage was always so.

The height of the P wave from the right atrium varied between 0·5 and 3·2 mv., with an average of 1·2 mv.; that from the left atrium between 0·4 and 4·8 mv., with an average of 2·0 mv.; and that from the left appendage between 0·4 and 3·6 mv., with an average of 2·2 mv. The average voltage of the P wave from the right atrium was one and a half times as large as in the control cases with carcinoma of the bronchus (0·7 mv.), but only half as large as in those with congenital heart disease (2·2 mv.). The average voltage of the P wave from the left atrium was twice that in the controls (1·0 mv.) and one and a half times that in the congenital heart cases (1·3 mv.) (Table I). There was no relation between the voltages of the P waves from the two chambers in individual cases.

The width of the P wave recorded from either atrium was usually only about two-thirds of that in the standard leads, because the deflection in either atrium appeared to be derived solely from that atrium. Occasionally the P wave in the direct tracing was as wide as that in the standard leads, and then this was usually due to a low wave before or after the main deflection that, judged by its timing, represented activity in the other atrium and could be recognized as such without difficulty (Fig. 3). In mitral stenosis the average width of the P wave was 0·086 sec. in the right atrial tracing, and 0·078 sec. in the left. These were slightly greater than the figures in the controls, which were respectively 0·077 and 0·071 sec. In the cases with congenital heart disease the P wave from the right atrium was 0·083 sec., but that from the left was only 0·06 sec. (Table I.)

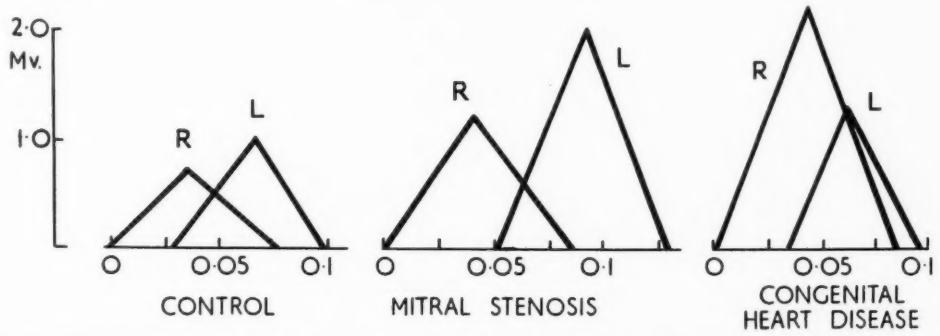

FIG. 1.—Diagrammatic representation of the relationship in size and time between the P waves in the right and left atrial electrograms of the control cases with carcinoma of the bronchus, cases with mitral stenosis, and those with congenital heart disease.

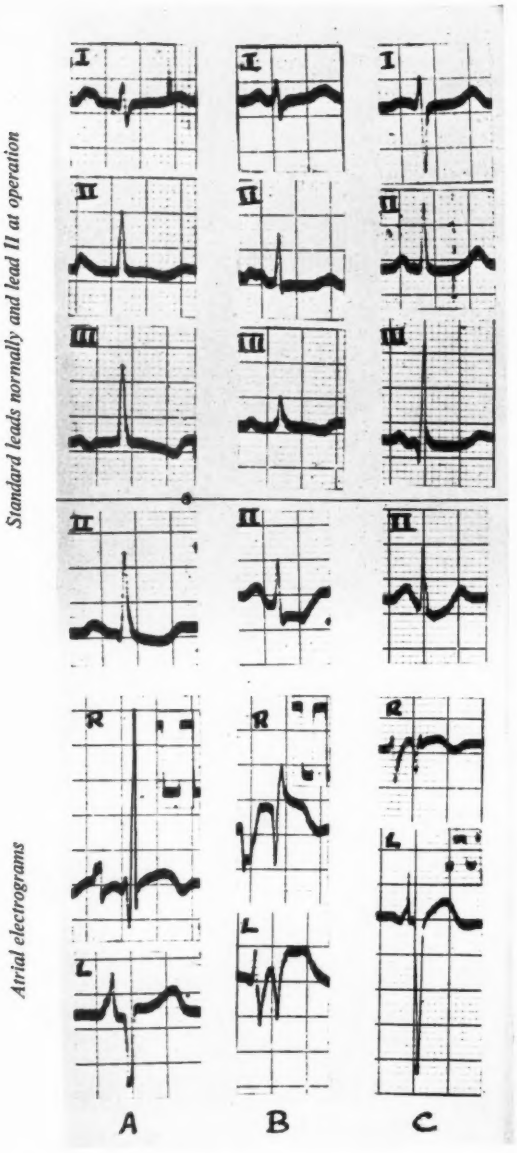

FIG. 2.—The three standard leads normally, standard lead II during operation, and the right and left atrial electrograms of three cases of mitral stenosis, showing by their different behaviour the individuality of the two components of the P waves in the standard leads and their correspondence in time with the P waves in the two atrial tracings. (Standardization, as indicated, is the same for both atrial electrograms of each case.)

The most striking difference between the tracings from the two atria in the cases of mitral stenosis was seen in their P–R intervals, and this was sometimes obvious at a casual glance. The intervals were always longer from the right than from the left atrium—in one case as much as double. The difference varied from 0·02 to 0·10 sec. and became greater as the P wave in the standard leads became wider and more notched. Moreover, whether the P–R intervals were measured from the beginning or peak of the P wave (ignoring in the left atrial tracings the small preceding wave from the right atrium when this was present) to the beginning or peak of the QRS complex, their difference was approximately the same as the difference between the two peaks or the standard P wave or between the edges of its plateau. Fig. 4 shows the good correlation between the difference of the P–R intervals (measured in (A) from the beginning and in (B) from the peak of the P waves to the beginning of the QRS complexes) and the distance separating the peaks of the standard P wave in that case. This indicates that the first peak corresponds to the right atrial P wave and the second to the left.

The average difference between the P–R intervals from the two atria in the cases of mitral stenosis, as measured from the beginning of the P wave to the beginning of the QRS complex, was 0·051 sec., and the average distance between the peaks of the standard P waves was also 0·051 sec. A similar correlation was present in the control group; here, however, the average difference between the P–R intervals was only 0·028 sec. and the distance between the peaks of the standard P waves was 0·031 sec. In the group with congenital heart lesions the average difference between the P–R intervals was 0·033 sec., but the peak to peak measurement of the standard P waves was only 0·018 sec. This was undoubtedly due to four of the eleven cases having no distinguishable second peak although the direct tracings showed asynchronous P waves: the discrepancy is caused by the peak of the left atrial P wave being hidden in the large P from the hypertrophied right atrium, which produces the tall, pointed P wave so characteristic of many of these conditions (Table I).

Tracings from the left atrial appendage were taken in 18 of the cases of mitral stenosis. The P wave was often very similar to that from the body of the left atrium, but usually more positive and its peak slightly later. Occasionally the peak of the predominant, positive deflection in the

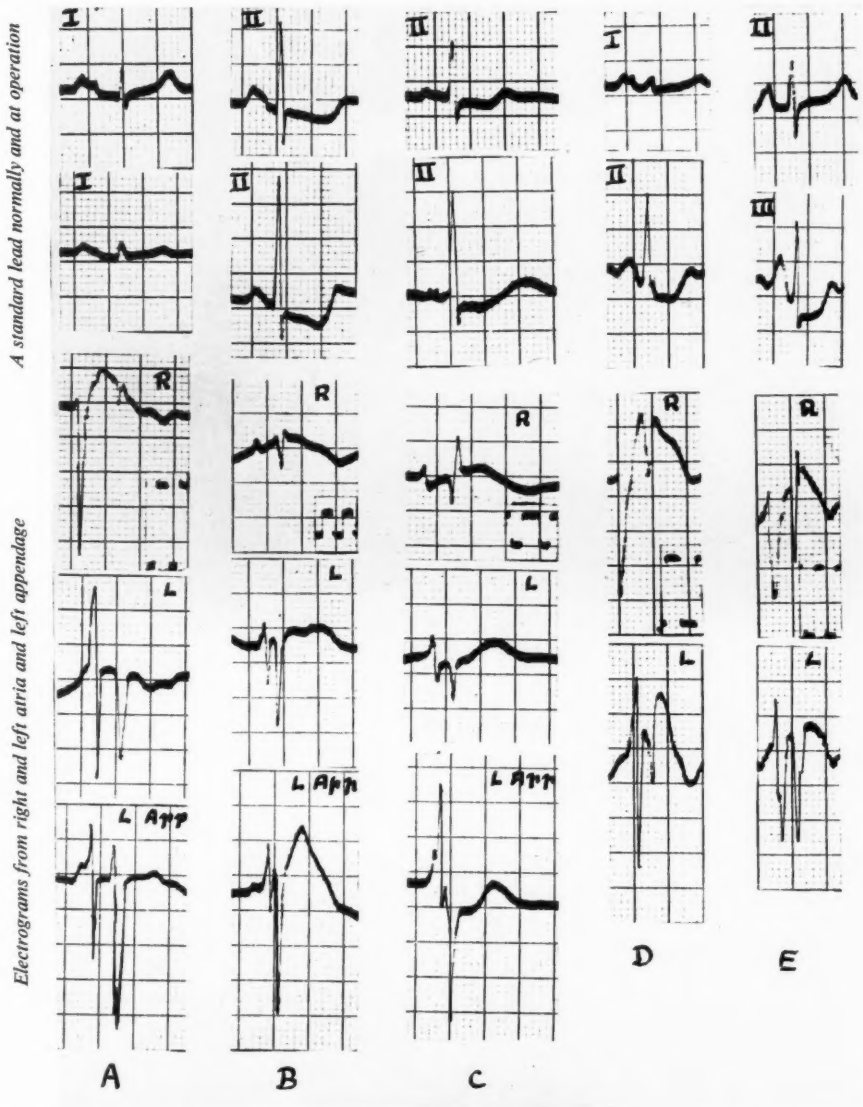

FIG. 3.—A standard lead normally and during operation, the right and left atrial electrograms in five cases of mitral stenosis, and the electrogram from the left atrial appendage in three of these, showing the relation between the two components of the standard P wave and the P waves in the right and left atrial electrograms. A small wave representing activity in the right atrium can be seen in the left atrial electrogram in (A) and (B). (Standardization, as indicated, is the same for all atrial electrograms of each case).

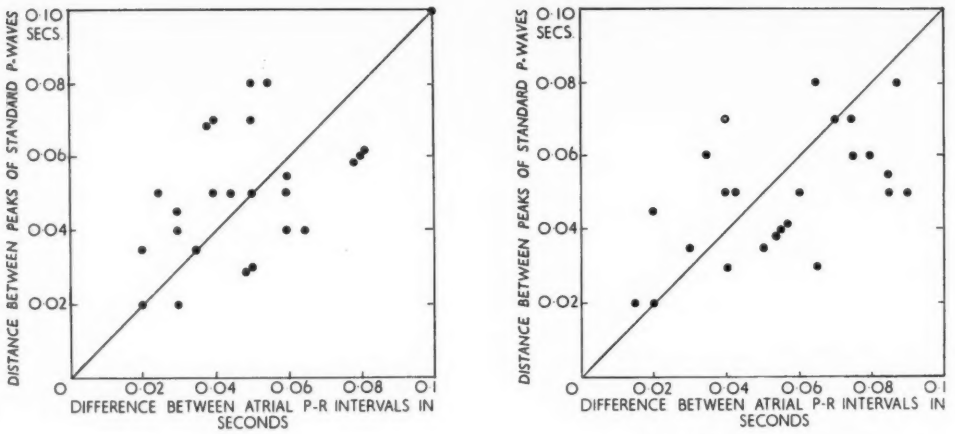

FIG. 4.—Showing the relation between the distance separating the two peaks of the P wave in the standard leads and the difference between the P–R intervals in the right and left atrial electrograms measured, in (A) from the onset of QRS and, in (B) from the peak of P to the onset of QRS, in 25 cases of mitral stenosis.

lead from the appendage corresponded to the peak of a smaller, negative deflection in the lead from the body of the left atrium (Fig. 3C).

A comparison between the difference of the P–R intervals from the two atrial tracings and the voltage of their P waves showed the average height of the left atrial P waves to be 1·6 mv. in the ten cases with the most asynchronism of the atria, and 2·5 mv. in the ten cases with the least asynchronism—a difference that is more than twice its standard error. The average height of the P waves from the right atria was similar in both these groups (Table II).

TABLE II

THE SIZE OF THE P WAVES, AND THE CARDIOTHORACIC RATIOS IN PATIENTS WITH DIFFERENT DEGREES OF ASYNCHRONISM OF THE RIGHT AND LEFT ATRIAL P WAVES

		Number of cases	P wave in standard leads		Height of P wave in atrial electrogram		Cardio-thoracic ratio
			Width (sec.)	Height (mv.)	Right atrium (mv.)	Left atrium (mv.)	
Degree of asynchronism in 25 cases of mitral stenosis (sec.)	More than 0·05	10	0·135	0·14	1·3	1·6	56·4
	0·05	5	0·116	0·18	0·9	1·8	58·6
	Less than 0·05	10	0·108	0·185	1·3	2·5	51·5

Comparison between the P waves in the standard leads and those in the direct atrial tracings showed that the former were taller where the voltage of the P waves was high in either of the atrial leads, though the difference was small (Table III). There was no relation between the widths of

the standard and atrial P waves, but the standard P waves were widest in those cases where asynchronism of the atria was greatest (Table II).

TABLE III

RELATIONSHIP OF HEIGHT OF P WAVES IN ATRIAL ELECTROGRAMS TO THAT IN THE STANDARD LEADS AND TO THE CARDIOTHORACIC RATIO, IN 25 CASES OF MITRAL STENOSIS

		Height of P waves in standard leads (mv.)	Cardio-thoracic ratio
High-voltage P waves in leads from	Both atria	0·175	52·7
	Left atrium	0·171	54·3
	Right atrium	0·175	55·0
	Neither atrium	0·142	56·2

Comparison of the voltage of the atrial P waves and the degree of their asynchronism with the pressures in the atria and pulmonary artery, whether taken at operation or during a previous catheterization, showed no correlation. In particular there was no correlation between the pressure and size of the P wave from the corresponding atrium.

Comparison of the voltage of the atrial P waves and the degree of their asynchronism with the clinical state of the patient showed no correlation with the length or degree of disability; there was a good correlation, however, with the cardiothoracic ratio (c.t.r.). The average c.t.r. was 56·4 in the ten cases with asynchronism of the atrial P waves above 0·05 sec., while it was only 51·5 in the ten cases with an asynchronism below 0·05 sec (Table II); and this difference is three times its standard error. On the other hand the c.t.r. was high in those cases where the voltage was low, and low in those where a high voltage was present in one, and particularly in both atrial tracings (Table III).

DISCUSSION

Several criticisms may be levelled against the significance given to these findings. The leads compared were not simultaneous tracings and so the time relation between them could not always be decided with complete certainty. Notching of the P waves in the standard leads was not always visible at the time the atrial tracings were taken, and the latter had, therefore, to be compared with a standard lead taken some time earlier. Multiple tracings from one atrium showed that the peak of the major deflection of the P wave was not reached at exactly the same time at all points on the atrium. But any errors introduced through these factors are thought to be more likely to diminish than to increase the evidence on which the significance of the findings is based.

There was sufficient correlation between the height of the P waves in the standard leads and those in the two atrial tracings to suggest that increase in the voltage of the P wave in either the right or left atrial electrogram will cause a larger P wave in the standard leads. But no exact correlation can be expected since the size of the P wave in the standard leads must also be influenced by the axis of the wave in relation to the frontal plane, and by the degree of overlapping, and therefore of summation, of its component parts—the atrial P waves.

The absence of any correlation between the width of the P waves in the standard leads and of those in the direct leads is not surprising for, as can be seen from Fig. 1, the width shown in the standard leads will depend more on the degree of asynchronism in the direct leads, and with this there is a good agreement.

The absence of any correlation between the voltage of the P waves in the direct leads and the atrial and pulmonary artery pressures may be compared with the lack of correlation between the size of the P waves in the standard leads and these pressures which was found by Trounce (1952) in similar cases of mitral stenosis.

Several points of interest have been demonstrated. First that the normal asynchronous appearance of the P waves in the right and left atrial electrograms—and, therefore, of the contraction of the atria, since " the order of excitation and contraction are identical " (Lewis, 1925)—is often increased in mitral stenosis and thus gives rise to the characteristic broad, notched P wave of this condition; and, moreover, that the two peaks of the notched wave correspond to the deflections from the right and left atria, the widening and notching revealing the double origin of the wave in the standard leads.

This double origin of the standard P wave can often be discerned, even in the normal cardiogram. Lewis and Gilder (1912) found that more than 30 per cent of normal P waves in lead II were notched, while Trendelenberg (1933) goes so far as to say that P II has always at least two peaks. Fredericq demonstrated as long ago as 1906 that in dogs the contractions of the atria were not synchronous, though Lewis (1925), while showing that the impulse reached the right atrium 0·021 sec., and finally the left appendage 0·045 sec., after its origin in the S-A node, stated that it was not true that the whole of the right atrium contracts before the left. Prinzmetal (1950), indeed, demonstrated synchronous contraction of the atrial appendages in dogs, and says that human atria behave similarly. But Levine *et al.* (1949) using intracardiac and œsophageal leads in man found that, although there may be some overlapping, the left atrium is stimulated 0·05 to 0·07 sec. later than the right; while Groedel and Borchardt (1948) using leads on the heart outside the pericardium also confirmed this asynchronism, though they put it at 0·03 to 0·04 sec. with which our figures are in better agreement. But it is doubtful whether it is generally recognized, as Lambert (1939) states that it is, that this asynchronism of the atrial contractions exists or that it is the cause of the notching of the standard P wave.

The dual origin of the standard P wave is well demonstrated by the different behaviour of the two components of the P waves in the standard leads (Fig. 2). In Fig. 2A the initial, right atrial half has a normal axis since it is positive in all three leads, while the later, left atrial component has a left axis deviation, being positive in lead I but negative in lead III. In Fig. 2B both components are positive in lead II, while that from the right atrium is flat in lead I and that from the left is flat in lead III. Fig. 2C shows almost complete separation of the two components of the P waves in leads II and III due to the striking difference in the P–R intervals that is seen in the atrial electrograms.

The excessive width of the " P mitrale " is generally recognized as being due to the increased time taken by the impulse to pass across the atria, though it remains undecided whether this is due to an enlarged left atrium (Wood, 1950), to local retardations in this atrium (Wenger and Hofmann-Credner, 1952), or to delayed inter-atrial conduction (Berconsky and Kloztman, 1945). If the P wave we have recorded directly from the left atrium represents the spread of the impulse through the wall of the whole of this chamber, the delay in its onset in cases where the P wave in the standard leads is widened suggests that the widening is due to a delay in the impulse reaching the left atrium. This might be due to dilatation of the right atrium, but there was no correlation between the asynchronism of the P waves in the two atrial tracings and the width of that from the right atrium; or it might be due to delay in conduction between the two atria. Fredericq (1906) found no evidence of specific conducting tissue between the atria in dogs; but Lewis *et al.* (1914) demonstrated in these animals a high rate of conduction between the region of the sino-atrial node and the left atrial appendage due to a straight band of fibres running between them; and Bachmann (1916) was able to increase the asynchronism of the atrial contractions three or four fold by crushing this inter-atrial band. No exactly similar structure is described in man; though here, too, the atrial musculature common to both chambers occurs in two localized groups (Walmsley, 1929), and " fairly direct fibres passing to the left auricle and to the auriculo-ventricular node excite these regions somewhat

in advance of the more distal regions of the right auricle itself simply because of the length of the pathway " (Fulton, 1949).

Alternatively, the P wave in the left atrial tracing may represent the impulse in only a limited area of the atrial wall, which becomes a relatively smaller part of the chamber as this increases in size; the delay in the onset of the P wave would then be due to the delay in the impulse reaching that part of the atrium from which the lead is taken, having first had to traverse other areas of the enlarged left atrium. The sharply defined onset of the P wave in most of the direct tracings, however, suggests that it represents the impulse throughout the atrium and that the increase in the asynchronism of the P waves in the right and left atrial electrograms is due to delay in the impulse reaching the left atrium. It is tempting to postulate that this is due to a naturally occurring lesion in some such inter-atrial band as that in which Bachmann (1916) produced similar changes experimentally in dogs.

Other points of interest are that the patients with the greatest asynchronism of the atria tended to have the lowest voltage of the P waves in the left atrial tracings and to have large hearts, while the patients with normal asynchronism of the atria were those who tended to have a high voltage of the P waves in the left atrial tracings and to have small hearts. These findings are only applicable to cases such as those investigated here, that is cases of mitral stenosis where the patient is sufficiently disabled to have operative treatment. In these the findings are not irrational. Left atrial hypertrophy might be expected in all cases of mitral stenosis. High voltage of the P wave in the left atrial tracings is evidence of this, but the converse—that normal or low-voltage P waves indicate no hypertrophy—is probably not true. It is more probable that the high-voltage P waves indicate a well functioning and the lower voltage a poorly functioning atrial myocardium (Berliner and Master, 1938), the latter perhaps due to the length of time or the severity of the increased work imposed on the muscle, or due to the effect of the past rheumatic infection. In many cases the conditions of the atrial and ventricular myocardium are likely to be similar. It is not surprising, therefore, to find little enlargement of the heart when the atrial electrogram, by a large P wave, shows evidence of a good atrial myocardium, and a large heart when there is evidence from a small P wave in the electrogram of a poor myocardium. Increased asynchronism is likely to occur from the same cause—a poor atrial myocardium—either directly due to a general or local slowing of conduction, or indirectly due to a lowered resistance to dilatation.

It is possible that the form of the P wave in the standard leads may be able to provide earlier information about the state of the myocardium than the cardio-thoracic ratio.

Summary

Electrograms have been taken from the outer surfaces of the right and left atria in 29 cases of mitral stenosis, 11 cases of congenital heart disease, and 8 control cases of carcinoma of the bronchus.

Compared with the control cases, the voltages of the P waves were increased in mitral stenosis especially in the left atrial tracings, and in congenital heart disease mainly in the right atrial tracings.

Asynchronism of the P waves in the right and left atrial tracings was present in every case. The average difference was 0·05 sec. in mitral stenosis, compared with 0·03 sec. in the controls and in congenital heart disease. This increased asynchronism accounts for the widening and notching of the P waves often seen in the standard leads of patients with mitral stenosis. The first peak is derived from the right atrium, the second from the left.

The voltage of the P wave in the left atrial electrogram was, on the average, significantly higher in patients with little or no cardiac enlargement; asynchronism of the P waves in the two atrial tracings was greater in those whose hearts were large. It appears that this asynchronism is likely to increase when the failure of the voltage of the left atrial P wave to increase suggests a poor atrial myocardium; and in these cases a high cardiothoracic ratio will often be present to suggest a poor ventricular myocardium also.

I wish to thank Mr. R. C. Brock and Mr. B. B. Milstein for their help in obtaining these records from hearts on which they were operating, Dr. Charles Baker for providing the clinical data and Dr. Albert Venner for the intracardiac pressures of these patients, and Dr. Maurice Campbell for his help in preparing this paper.

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FRANK WILSON

The news of the death of Frank N. Wilson has been received in this country with very real sorrow. There is wide recognition here of his important contributions to cardiology, and many British physicians have had the pleasure of meeting him, either in his own country or when he visited Britain. There are also many in this country who have had the privilege of working for a time as guests in his laboratory and have enjoyed not only his guidance and help but his continued friendship.

Dr. Wilson died on September 11, 1952, shortly before his sixty-second birthday. He received his medical education at the University of Michigan, and after service in Europe during the first World War, it was to that school at Ann Arbor he returned to pursue a career in teaching and research which has added lustre to its fame. Wilson was one of the young American doctors who came to work with Lewis during the 1914–18 war, and this association with the British master of cardiology not only greatly influenced his subsequent career, but led to a long-standing friendship. Later, when the United States of America entered the war Wilson left Colchester to serve with the U.S. Forces in France.

Returning to the U.S.A. he took up with enthusiasm the pursuit of cardiac research, and in his time he made contributions to electrocardiographic theory and practice as notable in their field as those of Lewis in his. Wilson published papers on practically every aspect of electrocardiography. Initially his work was on the arrhythmias and on bundle branch block. From the early 1920's onward he became more and more concerned with the ventricular complex and with the fundamental problems of the electrical manifestations of tissue activity. Much important work, experimental and mathematical, was on the recognition of the body as a volume conductor and on the conduction within that structure of action currents generated by the heart. Long before the modern intensive work on the vectorcardiogram, Wilson was dealing with three-dimensional vector problems.

It is now apparent that Wilson did for the analysis of the ventricular complex of the electrocardiogram what Lewis had done for the arrhythmias. He brought a fresh light to bear on the physical and physiological bases of the normal initial and final deflections, and he entirely changed our conceptions of the abnormal. His introduction of chest or præcordial leads, which had previously been used only sporadically for recording auricular activity, brought into clinical medicine a method that entirely revolutionized modern cardiographic practice.

In the early days, some twenty years ago, Wilson was content to face rejection of his theories by most of his colleagues, confident in the accuracy of the experimental work and the validity of his mathematical analysis: general acceptance of his views and results was, in fact, delayed for several years. The place of unipolar lead electrocardiography in medicine today is ample vindication of the accuracy and importance of his researches.

As one who had the privilege of working for a time as a member of his team, the writer would like to record his impressions of Wilson, the man. An indefatigable worker, whose sole aim in all he did was to seek scientific fact, he made no attempt to fit experimental data to a pre-arranged scheme, but revised hypotheses in the light of observations. One was impressed alike by the care and forethought which were given to the planning of crucial experiments, and by the judicial impartial spirit in which the results were scanned. Wilson's integrity was beyond question, and expediency was never allowed to influence his line of work or his attitude to experimental results. He never put his name to a paper that was not primarily his own conception and work. The large numbers of colleagues cited as co-authors (of whom on occasion the writer was one) are evidence of his

meticulous care that all who worked in his laboratory should share the credit of publication. Wilson did not reap where he had not sown, and any paper that bore his name was not only planned by him but almost in its entirety his own work.

The stranger entering his laboratory was given all the privileges of an honoured guest. All his papers, books, and lantern slides were put at the disposal of the colleague, however junior; he was given a master key to the laboratories, admitting him at any hour, and encouraged in every way to make full use of the opportunities afforded by the Heart Station. The whole atmosphere of the department took its tone from the Chief—happy, friendly, stimulating. He did not dwell in Olympian detachment, but shared a large office with his two chief assistants and with his guest. The blackboard and chalk were always at hand to demonstrate afresh some point in mathematics or physics which arose in discussion; his slides and records were filed at hand for reference and illustration; his broad experience and deep knowledge were always put at the student's disposal, patiently and modestly.

Wilson had interests outside medicine, and his particular hobby of bird photography was one that he adopted from his former chief, Lewis. Some miles from Ann Arbor he had a farm with fields of millet and other grain which were left unreaped as food for migrant birds; Stockbridge was a recognized bird sanctuary and visits there with him and his family were a rare pleasure.

His last years were clouded by illness—years of tedium and enforced inactivity that must have galled his active brain and spirit. It was a great pleasure for many of us in Britain that he and his wife were able to attend the International Conference of Physicians in London in 1947 so that a wide circle of European physicians could meet him and hear him speak.

Honours came to him at home and abroad—a Festschrift volume on his sixtieth birthday and the Gold Heart Medal of the American Heart Association: he was an Honorary Member of our British Cardiac Society and in 1950 the International Society of Cardiology nominated him as an Honorary Member. This was the first time such an honour was bestowed and the choice reflected the view of cardiologists the world over that he was the general constructor of much of modern electrocardiography.

Wilson was a charming chief, respected and admired by his staff and, for all his modesty and utter lack of pretension, a naturally accepted leader among his colleagues. There is no question that he is to be regarded as in the grand tradition of cardiologists, holding an honoured place among those who have laid the foundations of modern theory and practice in this branch of science.

IAN HILL

CASE REPORTS

A CASE OF SINGLE CORONARY ARTERY WITH STEREOGRAPHIC DEMONSTRATION OF THE ARTERIAL DISTRIBUTION

BY

P. J. D. SNOW

From the University Department of Cardiology, Manchester Royal Infirmary

A single coronary artery occurring as an isolated congenital defect is rare. It is unfortunate that some of the previous descriptions do not permit an accurate anatomical classification which would clarify the embryology of the anomaly. It is the purpose of this report, therefore, in recording a further case, to demonstrate the distribution of the vessel by stereoscopic radiographs, a method not previously used.

Case Report

A sixty-two-year-old male was admitted under the care of Professor Bramwell, with a peripheral neuropathy and congestive heart failure of six months' duration. The neuropathy and cardiac failure were thought to be related, but no diagnosis was established. Despite all treatment, the condition steadily deteriorated, death occurring six weeks after admission. At necropsy the heart weighed 600 g., both ventricles being hypertrophied. Only one coronary orifice could be found. This was situated in the right coronary sinus and had a lumen of 4 mm. It divided, 1 cm. from its origin, into two large branches passing anteriorly and posteriorly and one very small branch passing laterally towards the right ventricle which was thought to be a conus artery (Schlesinger *et al.*, 1949). In order to establish the presence or absence of an abnormal collateral circulation, cannulæ were passed down the main branches separately, but could not be passed into the smallest division: radiopaque medium was then injected using Schlesinger's (1938) technique. Mass injected into one branch issued from the other when the respective pressures were raised and lowered, indicating an anastomosis of abnormal size between these vessels. Stereoscopic radiographs of the entire heart were taken, after which the heart was unrolled and again radiographed. Stereodiagrams made from the original radiographs are shown in Fig. 1 together with a normal coronary tree for comparison.

Study of these radiographs showed that the posterior division corresponded to the right artery and, in addition to the right ventricle, supplied a considerable part of the posterior wall of the left, representing to a striking degree the preponderant right coronary pattern of Schlesinger (1940). The anterior division passed downward through the upper part of the septum, between the pulmonary artery and aorta, to reach the interventricular groove: here it divided into upper and lower branches corresponding to circumflex and anterior descending branches. No occlusions were visible on the radiographs and dissection of the vessels revealed only moderate atheroma. The abnormal anastomosis was attributed to ventricular hypertrophy.

Histological examination of the myocardium revealed that the enlargement was due to extensive amyloid deposits. These were also present in the peripheral nerves, tongue, and spleen. Primary amyloidosis affecting the peripheral nerves and myocardium and severe enough to cause congestive failure is very uncommon and will be the subject of a separate report.

Discussion

Smith (1950) defined a single coronary artery as one arising from an arterial trunk by a single ostium and supplying the whole heart regardless of distribution. He was able to collect 45 such cases, including two of his own. Thirteen of these were known to have other congenital cardiac defects.

The origin of the condition is of some embryological interest, and both Smith (1950) and Krumbhaar and Ehrich (1938) recognized three types: (1) those in which a single artery after supplying one

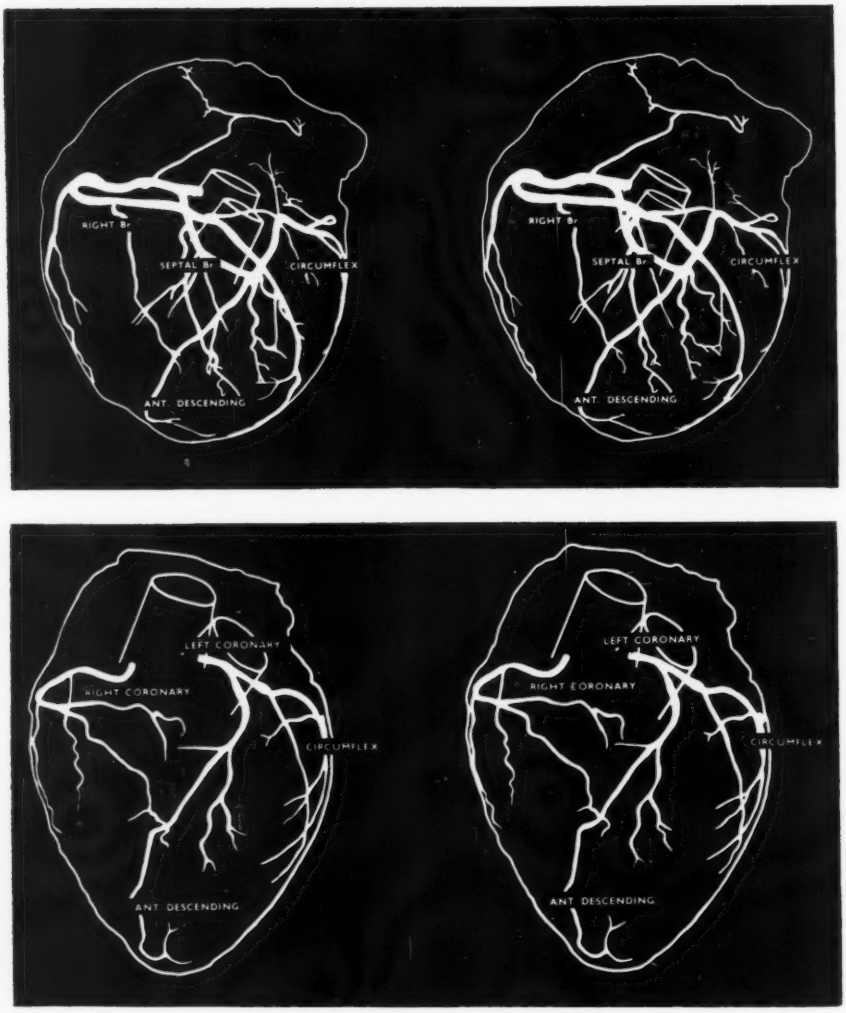

FIG. 1.—Stereodiagrams showing the coronary tree of the case described (A) and of a normal heart (B). Many observers are able to view stereographic pairs without a stereoscope. The page should be held at about fifteen inches from the eyes and the visual accommodation relaxed as if to view an object at infinity, so that the visual axes are parallel.

If the page is now brought slowly into focus, each eye will view its own member of the stereographic pair: three images are perceived, of which the centre one is due to the fused pair. This will appear three dimensional.

ventricle, continues on to supply the other, (2) those in which a common trunk divides so that the distribution of both left and right arteries are represented, and (3) those in which the distribution was so atypical that it was comparable with neither left nor right coronary artery.

Although Hyrtl (1882) accepted only cases of the first type as examples of absent coronary

artery, it does not follow, as he suggests, that the rest are merely anomalies of origin. The present case belongs to group (2), in which it is uncertain if the apparently missing artery is really absent, or merely has an anomalous origin. It has been suggested that a branch of the solitary vessel may take on the course and distribution of the absent artery thus simulating a misplaced origin (Sanes, 1937; Speer, 1938; and Roberts, 1947). Both types may be represented in this group and a more detailed anatomical classification is likely to assist in the distinction. Clear depiction of the coronary tree in each case is of obvious importance, yet no suitable method for demonstrating or recording the anomaly has previously been used. Verbal descriptions, in an attempt to avoid ambiguity, become lengthy and involved, and two-dimensional diagrams are not always satisfactory. A more graphic method is obviously desirable and it is suggested that stereoscopic radiography of the injected heart is the most accurate.

As an isolated congenital defect, a single coronary artery does not significantly affect the chance of survival. In Smith's series, of 31 patients with no known associated defects, only 2 did not reach adult life, dying of bronchopneumonia at three days and three months old. Of the remaining cases in which the ages are known, 10 died before the end of the fourth decade and 19 before the end of the sixth; 8 others survived over the age of sixty. When associated with other congenital defects, however, only one out of thirteen reached adult life, the defect in this case being a bicuspid aortic valve. The majority of these cases possess a grossly atypical arterial distribution and belong to group (3). Acquired cardiac lesions were found in 9 of the 30 adult cases, including 4 with coronary occlusion and infarction. Roberts and Loube (1947) believed the effects of occlusion to be severe since available anastomoses had already been utilized to compensate for the defective arterial distribution. A more likely explanation is the lack of a second coronary artery to provide a collateral circulation.

Summary

A case of single coronary artery occurring as an isolated congenital defect is demonstrated by radiopaque injection and stereoscopic radiography. The developmental types of single coronary artery and the effect of the anomaly on survival are discussed.

I wish to thank Professor Crighton Bramwell for his permission to publish this case, and also the Department of Medical Photography for assistance in preparing the stereo-diagrams.

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CARDIO-AORTIC INVOLVEMENT IN CONGENITAL SYPHILIS WITH CO-EXISTENT RHEUMATIC HEART DISEASE

BY

F. J. T. BOWIE AND R. G. SIMPSON

From the Royal Infirmary, Aberdeen

A familiar and not uncommon clinical problem is provided when a patient presents with signs of aortic incompetence together with a history of rheumatic fever and a positive serological test for syphilis. The cause of the aortic valve lesion usually rests between syphilis and rheumatism, and the diagnosis will swing in one direction or the other according to the presence or absence of collateral signs of the respective diseases. If such a patient also shows unequivocal evidence of mitral stenosis, the cause of the combined lesions may reasonably be attributed to rheumatic heart disease. Likewise, the co-existence of an aneurysm of the thoracic aorta and aortic incompetence strongly suggests a comprehensive diagnosis of cardio-aortic syphilis. Occasionally, the possibility of combined syphilitic and rheumatic heart disease must be considered, albeit such a combination is uncommon.

The essential features of the case to be described were aortic regurgitation, fusiform aneurysm of the ascending aorta and a persistently positive blood Wassermann reaction. A diagnostic exercise was set by the fact that the aortic valve lesion became manifest about two months after an attack of rheumatic fever, the aneurysm being detected for the first time 18 years later. Further, the patient was known to be a subject of congenital syphilis.

Case Report

The patient, a former electricity inspector, 38 years of age, was admitted to Aberdeen Royal Infirmary in 1949, on account of exacerbation of pain from chronic duodenal ulceration. Symptoms of dyspepsia first appeared at the age of 19 years, followed a few months later by an acute perforation, which was treated by surgical repair and gastroenterostomy. The ensuing years of reasonably good health were interrupted by bouts of ulcer dyspepsia which in recent months had become more troublesome.

Past History. At the age of 19 years, in 1930, the patient was admitted to a hospital in Aberdeen on account of pyrexia, joint pains, and nodular erythema of the extremities, of some three weeks' duration. A diagnosis of rheumatic fever was made, and the symptoms settled promptly during salicylate therapy. About two months later clinical evidence of aortic insufficiency was detected. Less than one year after the first rheumatic episode, he was re-admitted to the same hospital, because of similar symptoms; these responded as before to treatment with salicylates. Clinical signs of aortic incompetence were still present, and an X-ray film of the chest was reported as showing a normal heart shadow. In 1944, the patient was admitted to hospital because of dyspeptic symptoms and was diagnosed as chronic duodenal ulcer and aortic incompetence. An X-ray report stated: " Moderately severe enlargement of left ventricle and an aortic arch of normal appearance." Systematic interrogation disclosed that since 1944 or thereby there had been gradually increasing effort dyspnœa and palpitations; there had also been paroxysms of breathlessness at night during recent months. The family history, as obtained at the time of admission, disclosed nothing remarkable. The patient had been married for 3 years and his wife and three young children enjoyed good health.

Physical examination. The patient was well-developed and well-nourished and did not look ill. The temperature was 98·4° F., the pulse rate 90, and the respiration rate 20 per minute. Apart from a number of fine radiate scars above the upper lip, the face, skin, head, nose, ears, and mouth showed nothing of note. Eye movements, pupils and optic fundi were normal. The trachea was in the mid-line. Both sides of the chest expanded equally, and the percussion notes and breath sounds were normal. The radial pulses were equal and regular and were of the " water-hammer " type, and the blood pressure was 145/50. The apex

beat was in the sixth interspace, outside the mid-clavicular line, and had a heaving quality. A faint and localized pulsation was felt in the second right interspace close to the sternum; from that site a grade-two systolic murmur was conducted upwards towards the neck, and a blowing diastolic murmur downwards alongside the sternum. A low-pitched diastolic rumble was heard in the region of the apex beat. There were no signs of congestive heart failure. The liver, spleen, and kidneys could not be palpated. The genitalia were normal, and detailed examination of the nervous system did not reveal any significant abnormalities.

Laboratory studies. The blood Wassermann and Kahn reactions were strongly positive on several occasions. Spinal fluid obtained by lumbar puncture showed normal cytology and chemistry and gave a negative Wassermann reaction. The urine was free from albumin and sugar and there was no organized deposit. The electrocardiogram was normal.

Radiological findings. A barium meal showed gross deformity of the duodenal cap and an ulcer crater. Plain films and screen examination of the chest showed enlargement of the left ventricle and an aneurysmal bulging of the ascending portion of the aortic arch, with some linear calcification (Fig. 1) and very obvious pulsation. The only deformity or displacement of the œsophagus shown by a barium swallow was that caused by an enlarged aorta.

Clinical diagnosis: Chronic duodenal ulcer; aortic aneurysm (luetic); aortic regurgitation (? rheumatic ? luetic). At this juncture the patient was seen by one of us (F.B.) in consultation and, as a result of this, the following additional information was disclosed.

Synopsis of luetic history. During the patient's first episode of rheumatic fever in 1930, a routine blood Wassermann test was found to be strongly positive. There was at that time no history or other evidence of

FIG. 1.—Radiogram showing aneurysm and linear calcification in ascending aorta. Right lateral view.

acquired infection and no knowledge of syphilis in the patient's family. There were no unequivocal signs of congenital syphilis, but the incisor teeth were rather small and deformed and there were circumoral rhagades. A diagnosis of congenital lues was made on the grounds of a repeatedly positive blood reaction in a youth of 19 with no evidence of acquired disease and with stigmata suggestive of congenital infection. Treatment was commenced with injections of bismuth, and was carried on intermittently until 1937, eight courses in all being given. The blood Wassermann reaction remained strongly positive throughout that period. The patient defaulted in 1938 and returned to the Clinic in 1942 with acute gonorrhœa. The blood Wassermann was still strongly positive, and treatment was resumed with a course of mercury sulphide, but he defaulted again a few months later and did not return.

Further evidence in support of the diagnosis of congenital syphilis has recently been obtained from case records which show that the patient's father, then aged 33, attended at the Clinic in the year 1917 for treatment of late syphilis; he defaulted in the following year, but returned for further treatment in 1932. The patient's sister, his only sibling and by three years his elder, is a known subject of congenital syphilis; she has been married for 22 years, and has a married daughter aged 21 years. Nothing is known about the patient's mother beyond the fact that she left the home in 1917 never to return. The patient himself has been twice married: the first marriage lasted from 1933 to 1941 and was sterile; in 1946 he married a widow who has presented him with three healthy offspring, whose present ages range from four months to four years.

Discussion

A stand must be taken upon the two issues which are in debate. The first concerns the cause of the aortic valve defect; the presumption of a rheumatic origin is based on the history of two attacks of rheumatic fever in youth and the development of auscultatory evidence of aortic regurgitation two months after the initial episode.

The second issue concerns the cause of the aortic aneurysm and demands more detailed consideration. Strong evidence is necessary to enable one to decide which of the two diseases—rheumatism or congenital syphilis—was responsible for the aortic lesion, since both are generally regarded as rare and disputable causes of aneurysm. Such evidence is provided by the radiograms which showed linear calcification in the walls of the aneurysm, a condition indicative of syphilitic aortitis. According to Shanks and Kerley (1951) calcified plaques in the ascending aorta are diagnostic of syphilis, a view which has been confirmed in recent years by the extensive clinical, pathological, and radiological investigations of several American authors (Jackman and Lubert, 1945; Leighton, 1948; and Thorner *et al.*, 1949). The significance of this sign is further enhanced when calcification is absent from other portions of the aorta, and when the subject is less than fifty years of age. Calcification tends to occur in those cases where syphilis is of long duration, and consequently indicates relatively mild and very chronic aortitis. It is concluded that the weight of evidence in the present case is sufficient to permit a clinical diagnosis of combined chronic rheumatic and congenital syphilitic heart disease.

Summary

The case is described of a man, aged 38 years, with signs of aortic incompetence and of thoracic aortic aneurysm. Evidence is adduced whereby the aortic valve lesion is attributed to rheumatic heart disease, the aneurysm to congenital syphilis.

Linear calcification of the ascending portion of the aorta has been demonstrated radiologically, and the significance of this sign is discussed.

We wish to thank Professor H. W. Fullerton, Physician, Aberdeen Royal Infirmary, for permission to publish this case. We are also indebted to Miss Grace Barclay, Woodend Hospital, for the photographic reproduction.

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ABSTRACTS OF CARDIOLOGY

EDITED BY J. L. LOVIBOND

A Comparative Study of the Effects of Veratrum Viride and Tetraethylammonium Chloride in Hypertension. A. P. SHAPIRO, A. A. BRUST, and E. B. FERRIS. *Ann. intern. Med.*, **36**, 807–810, March, 1952.

At the Cincinnati General Hospital 15 patients with hypertension were studied; the hypertension was benign in 11, malignant in 3, and due to chronic pyelonephritis in 1. Tetraethylammonium chloride was given in a dose of 400 mg. and 0·2 ml. of " veratrone " (veratrum viride) was given intravenously 1½ to 2 hours later. The fall in blood pressure was of an equal degree with either drug.

Arthur Willcox

Ligation of the Vena Cava in the Treatment of Heart Failure. P. COSSIO. *Amer. Heart J.*, **43**, 97–102, Jan., 1952.

Over a period of two years the author observed in detail 90 cases in which ligation of the inferior vena cava was carried out for uncontrollable heart failure. The surgical mortality was initially 25%; it was soon reduced to 6%. Early improvement, sometimes most surprising, was observed in 70% of the patients and was maintained for months or even years in 56%, provided medical treatment was continued. The early improvement is attributed to the reduction of blood return to the heart and the later improvement to the formation of a lake of blood with a slower return in the recumbent position and also to the elimination of the source of microemboli.—[Author's summary.]

Alcohol Vapor by Inhalation in the Treatment of Acute Pulmonary Edema. A. A. LUISADA, M. A. GOLDMANN, and R. WEYL. *Circulation*, **5**, 363–369, March, 1952.

Alcohol has been administered by inhalation to patients in attacks of pulmonary œdema because of its " antifoaming " action. For this purpose 100% oxygen was passed through 95% alcohol which had been vaporized into a fog, and given through a nasal catheter. This method allowed the patient to expectorate. In healthy subjects insignificant changes in pulse rate and blood pressure were recorded, and there was slight euphoria. The serum concentration of alcohol was less than 10 mg. per 100 ml. When the vapour inhalations were given in 17 attacks of pulmonary œdema, of which 7 were very severe, great relief resulted immediately in 10 and some improvement in 5 more. In the 2 failures the patient objected to the alcohol.

C. W. C. Bain

Chest Pain in Association with Pulmonary Hypertension. Its Similarity to the Pain of Coronary Disease. W. N. VIAR and T. R. HARRISON. *Circulation*, **5**, 1–11, Jan., 1952.

The authors describe 6 cases in which the patient had chest pain which might have been attributed to coronary disease. The ætiological diagnoses were: atrial septal defect, chronic cor pulmonale (3 cases), massive pulmonary embolism, and mitral valve disease. Necropsy in 3 of the cases showed no evidence of coronary disease. Although the pulmonary arterial pressure was not measured in any of the cases and there was no other factual support, the pain was attributed to distension of the pulmonary artery secondary to pulmonary hypertension.

Paul Wood

Effort Syncope as an Early Manifestation of Primary Pulmonary Hypertension. W. DRESSLER. *Amer. J. med. Sci.*, **223**, 131–143, Feb., 1952.

The author reviews 6 reported cases and describes 3 others in which syncope precipitated by effort was the chief sign of primary pulmonary hypertension. He states that this symptom combined with dilatation of the pulmonary artery, accentuation and splitting of the pulmonary second sound, and evidence of right ventricular hypertrophy, should suggest the diagnosis. Syncope may often appear before symptoms of congestive cardiac failure develop. Cyanosis is not an invariable feature of the condition.

G. S. Crockett

An Anomalous Coronary Artery Arising from the Pulmonary Artery. E. S. CRONK, J. G. SINCLAIR, and R. H. RIGDON. *Amer. Heart J.*, **42**, 906–911, Dec., 1951.

A third case is reported in which the right coronary artery arose from the pulmonary artery, only two such cases having previously been reported in the literature. This patient died at 90 years of age and the condition was found at necropsy; the other two had reached adult life, dying at 30 and 61 years of age respectively. The embryology of this and other similar anomalous coronary-artery malformations is fully discussed.

T. Semple

Left Coronary Artery from the Pulmonary Artery. Three Cases, One with Cardiac Tamponade. H. I. MCKINLEY, J. ANDREWS, and C. A. NEILL. *Pediatrics*, **8**, 828–840, Dec., 1951.

The authors report from the Hospital for Sick Children, Toronto, 3 new cases in which the left coronary artery arose from the pulmonary artery, bringing the total of reported cases to 35. In one of the present cases there was myocardial rupture, which has not previously been recorded in this condition. The diagnosis was made before death in all 3 cases with the aid of X rays and the electrocardiogram, which showed a low-voltage tracing, inverted T waves in leads I and III, and a variable degree of left axis deviation. (The diagnosis was similarly made before death in 5 of the 11 cases reported since 1947.) The symptom pattern is one of feeding difficulty at the second or third month of life for which no obvious cause can be found, then intermittent dyspnœa with exertion, and in some cases cardiac angina, which is well

and fully described. The desirability of recognition of this pattern is emphasized, as early diagnosis before irreversible myocardial damage has occurred might enable new methods of treatment to be applied, such as the use of vasodilator drugs or surgical measures to increase the left coronary flow by raising the pulmonary pressure, as by the Potts-Smith operation.

David Morris

Local Circulatory Changes Associated with Clubbing of the Fingers and Toes. G. M. WILSON. *Quart. J. Med.*, **21**, 201–213, April, 1952.

This investigation was made to test the postulate that clubbing of the fingers and toes is primarily a manifestation of a peripheral circulatory disorder. The blood flow in the affected digits was measured by the heat elimination method of Stewart, which involves the use of a calorimeter.

An increase of blood flow was demonstrated in cases of clubbing due to congenital heart disease, subacute bacterial endocarditis, and pulmonary disease. This increase of blood flow did not appear to be due to vasodilator nervous action as it was unaffected by procaine-induced nerve block. In 2 cases of unilateral clubbing due to arteriovenous fistulæ the blood flow was greater in the affected than in the normal digits. A reduction of the circulation to the fingers led to a regression of the clubbing; this was shown in 2 cases in which the main artery to the limb was ligated. The regression in finger-clubbing seen after successful treatment of underlying thoracic disease was also associated with a decrease in blood flow.

The author discusses the relationship between the increased blood flow and the structural changes in the clubbed digits, and concludes that in unilateral cases clubbing is due to physical abnormalities in the arterial tree, while in bilateral cases " it is probably a result of generalized circulatory disturbance not yet fully understood."

Albert Venner

The Treatment of Intermittent Claudication. N. HAMILTON and G. M. WILSON. *Quart. J. Med.*, **21**, 169–183, April, 1952.

A critical evaluation of the effect of the current remedies for intermittent claudication has been made in a series of 40 patients.

In patients confined to bed, treatment by intermittent venous occlusion resulted in improvement, but it was no greater than that which occurred in an initial period of bed rest; or in other cases, no greater in a treated as compared with an untreated limb that received the effects of bed rest alone. Intermittent venous occlusion unaccompanied by bed rest did not produce improvement. None of their patients treated with α-tocopherol, tolazoline (priscol), methyl testosterone, or dihydroergotamine showed any improvement in exercise tolerance which could be confidently regarded as due to the treatment. Lumbar sympathectomy was performed in only 2 cases, in order to avert gangrene, which it successfully did. Tenotomy performed on 4 cases gave relief of pain in all, although in one case the disability from the operation was considered to be as great as that from the original complaint.

The effect of single doses of glyceryl trinitrite, adrenaline, nicotinic acid, tetraethylammonium bromide, tolazoline, dihydroergotamine and padutin was compared with that of a placebo. No consistent improvement in exercise tolerance following administration of any of these drugs could be demonstrated.

Albert Venner

Some Limitations of Lumbar Sympathectomy in Arteriosclerosis Obliterans. Early Results in One Hundred Consecutive Cases. R. G. SMITH, M. GULLICKSON, and D. A. CAMPBELL. *Arch. Surg., Chicago*, **64**, 103–107, Jan., 1952.

The results of unilateral lumbar sympathectomy in 100 cases of arteriosclerotic disease of the lower limb in a total of 83 patients are analysed.

It is concluded that 52% of the patients did not benefit from the operation and that sympathectomy holds little promise of saving the limb in the following circumstances: (1) when gangrene follows obstruction of the femoral or popliteal artery; (2) when there is severe rest pain accompanied by œdema and inability to tolerate the limb in the horizontal position; and (3) when sympathetic block produces a fall in the skin temperature of the extremity. Useful results were obtained in 45 out of 66 patients who survived without loss of the limb.

C. J. Longland

Experimental Studies on Reversal of the Circulation in the Lower Extremity. T. H. PALMER and C. S. WELCH. *Surg. Obstet. Gynec.*, **94**, 206–214, Feb., 1952.

The experiments described were designed to test the possibility of maintaining the nutrition of a limb when the arterial stream is diverted into the veins in an attempt to reverse the circulation. The femoral vessels in 48 dogs were divided and the proximal cut end of the artery was anastomosed by suture to the distal cut end of the vein.

It is concluded from these experiments that true reversal of the circulation does not occur when the arterial blood is shunted into the companion vein and that a state of affairs resembling an arterio-venous fistula ensues. The distal part of the limb is deprived of blood and gross œdema is produced; this œdema is due to the transmission of the high arterial pressure to the capillaries without the intervention of the arterioles.

C. J. Longland

The Auricular Arrhythmias. MYRON PRINZMETAL, M.D., ELIOT CORDAY, M.D., ISIDOR C. BRILL, M.D., ROBERT W. OBLATH, M.D., H. E. KRUGER, and Associate Authors. Springfield, Illinois, U.S.A., Charles C. Thomas, 1952. Pp. 387. £6. (Blackwell Scientific Publications, Oxford.)

Prinzmetal's researches, developed during the past 4 years with colleagues at Los Angeles, have resulted in important conclusions, now widely accepted. The study of auricular motion by means of the high-speed cinematograph and the cathode-ray oscillograph enabled him to establish beyond reasonable doubt that all types of auricular arrhythmia have the same mechanism, originating from impulse discharges in ectopic auricular foci. The old theory of circus movement is no longer

tenable. In this monograph we can follow and understand clearly the logical development of these arguments and visualize the fascinating experimental work on which they are based. The clinical application of this new conception of auricular activity is carefully correlated with events known to occur in patients; current knowledge on practical therapy is covered. Clarity of statement and presentation, careful summarizing at every stage, and graphic illustration are some of the noteworthy features of this important production, which is a tribute to authors and publisher alike. *J. L. Lovibond*

Angiocardiography. Vol. XX, Annals of Roentgenology. CHARLES T. DOTTER, Assistant Professor of Radiology, Cornell Univ. Med. Coll., and ISRAEL STEINBERG, Assistant Clin. Professor of Radiology and Medicine, Cornell Univ. Med. Coll. London, Cassel & Co., Ltd., 1952. Pp. 304, Illus. 635, Figs. 252. £5 18*s.* 6*d.*

The addition of this volume to the well-known series of atlas radiological monographs will be welcomed. By the familiar technique of illustrative outline drawings, the information is set out clearly and the text is direct and easy to follow. Angiocardiographic procedure is described, and due emphasis is laid on its limitations in the cyanotic child. A long and useful chapter is devoted to the normal angiocardiogram. The varieties of heart disease, congenital and acquired, common and rare, are all covered fully. There is an illuminating section on pulmonary tumours and the authors recommend that it should become a routine part of the assessment in all such cases. Adequate references and indexing complete a satisfactory work. *J. L. Lovibond*

Leonardo da Vinci, on Movement of the Heart and Blood. K. D. KEELE, M.D., F.R.C.P. London, Harvey & Blythe Ltd., 1952. Pp. 142, Figs. 68. £4 4*s.* 0*d.*

Leonardo's original and inventive genius lent themselves well to the study of human anatomy. The accuracy of his versatile observations provide a wealthy contribution to cardiovascular physiology. Although some of his deductions were faulty, he believed, for example, that the right pulmonary veins normally entered the right auricle and that the two ventricles were connected by pores in the inter-ventricular septum, he has handed down many great achievements. To mention one only, his admirable description of the mechanism of the aortic and tricuspid valves, deduced without the help of vivisection, is a masterly observation. Dr. Keele has brought vividly to light much of what might have been passed over and presents his subject with a lively interpretation and respect. *J. L. Lovibond*

Disorders of the Heart and Circulation. Edited by R. L. LEVY, M.D. London, Baillière, Tindall & Cox, 1951. Pp. xvi +944, 368 Figs. 91*s.* 6*d.*

The chapters on cardiovascular disease which appeared first in Nelson's loose-leaf Medicine have now been collected together into a single volume, re-edited, revised and added to. Maude Abbot's original section on Congenital Heart Disease is included, and 41 authors co-operate in this work. The articles by Levy on Coronary Insufficiency, by D. W. Richards on Circulatory Physiology, and by A. Graybiel on Electrocardiography are some of the better contributions. Repetition has not entirely been overcome and the index is confusing. *J. L. Lovibond*

Accelerated Conduction. The Wolff–Parkinson–White Syndrome and Related Conditions. MYRON PRINZMETAL, M.D., REXFORD KENNAMER, M.D., ELIOT CORDAY, M.D., JOHN A. OSBORNE, M.D., JOSHUA FIELDS, M.D., and L. ALLEN SMITH, M.D. New York, Grune & Stratton, 1952. Pp. 110, Figs. 48. $4.

By applying to ventricular movement their technique of high-speed cinematography and simultaneous electrocardiography these authors have distinguished two types of WPW aberration, nodal and ventricular. The former is commoner, and they produce evidence to favour a nodal lesion which diminishes delay of the normal excitation wave in the A-V node; hence "accelerated conduction." There is little to support the hypothesis of an accessory conducting system. They conclude that the WPW complex is composed of a premature localized contraction in one ventricle fused with the normal contraction of the rest of the ventricular mass.
J. L. Lovibond

Atlas der Elektrokardiographie. O. RITTER and V. FATTORUSSO. Basel and New York, S. Karger Ltd., 1951. Pp. 256, Figs. 219. Sfrcs. 35 (about –3).

This book was written as an introduction to clinical electrocardiography for students and doctors and is based on a rich material mostly collected in different American and European clinics. The authors can be congratulated on giving a unitarian and well-balanced exposition of their different views, presenting the best material which each of these schools could offer. The book opens with a note of warning on the shortcomings of electrocardiography, particularly concerning prognosis. It includes a useful chapter on the electrocardiogram in children and infants, and is richly illustrated with electrocardiographic drawings, replicas of technically perfect records; it is produced on the lines of Graybiel and White's atlas. The diagrams explaining the epicardial genesis of pathological Q waves in cardiac infarction are especially clear and excellent for teaching purposes, but the insistence on the different patterns of current of injury and current of ischæmia must be misleading for the beginner. This atlas includes 50 references of electrocardiographic "classics" mostly of American and German origin; the only British reference is Lewis's book. *C. Papp*

The Treatment of Angina Pectoris with Khellin. J. J. CONN, R. W. KISSANCE, R. A. KOONS, and T. E. CLARK. *Ann. intern. Med.*, **36**, 1173–1178, May, 1952.

At the White Cross Hospital, Columbus, Ohio, 42 patients with angina pectoris were treated with khellin for

periods averaging 6 months, and the clinical response was gauged by the number and severity of anginal attacks. Of these patients 30 had a favourable response to the drug, with a decrease in the number and/or severity of the anginal pains; 6 patients were unchanged, and 3 developed an increase of cardiac pain; 3 patients died during the course of treatment. One or more undesirable reactions, including nausea, sometimes accompanied by vomiting, loss of appetite, epigastric pain, insomnia, and tachycardia were observed in 26 of the patients.

The authors still prefer nitrites in the routine treatment of angina, but think that khellin may be useful in patients who fail to respond to the usual type of therapy. The dose used was one 20-mg. tablet per day for the first week, increasing to 2 a day in the second week, and thereafter increased at weekly intervals by 1 tablet a day until a response or reaction took place. *J. McMichael*

Stenosing Coronary Arteritis: its Possible Role in Coronary Artery Disease. F. G. ZAK, M. HELPERN, and D. ADLERSBERG. *Angiology*, **3**, 289–305, Aug., 1952.

Among 50 fatal cases of coronary artery disease, all in subjects under 46 years of age, the authors encountered one in a man of 27 with acute tonsillitis. At necropsy the heart showed a large anterior infarct, though atheroma was mild. A thrombus was associated with eccentric narrowing of the descending branch of the left coronary artery.

A further series of 25 fatal cases, in which the patients' ages ranged from 25 to 40 years, were studied histologically. In 7 of these there were typical lesions of acute coronary arteritis and in 6 further cases one or more of these lesions were observed.

The authors point out that several attacks of acute arteritis are necessary to produce sufficient stenosis for a thrombus to occlude the main lumen.

Peter Harvey

Factors in the Onset of Coronary Occlusion and Insufficiency. Effort, Occupation, Trauma, and Emotion. A. M. MASTER and H. L. JAFFE. *J. Amer. med. Ass.*, **148**, 794–798, March 8, 1952.

A study of 2080 attacks of acute coronary occlusion and 100 episodes of acute coronary insufficiency, revealed that these can be differentiated by cardiographic investigation in 95% of cases. Through-and-through infarction results from coronary occlusion, whereas coronary insufficiency produces only subendocardial necrosis. The authors were concerned with the relationships of these conditions to exertion. They found that unusual effort was present in only 2% of the cases of occlusion, but there was a relationship to effort, or to factors increasing the work of the heart, in about half the cases of coronary insufficiency. They formed the impression that the prognosis is much better than was formerly thought; about half to two-thirds of cases of occlusion return to gainful employment within a year, and the authors consider that the outlook in coronary insufficiency is even better.

James W. Brown

Revascularization of the Heart by a Pedicle Skin Flap. J. VON WEDEL, P. W. STONE, C. G. NEUMANN, J. W. LORD, J. W. HINTON, and R. E. MORAN. *Science*, **116**, 319–320, Sept. 26, 1952.

A series of experiments were carried out in 25 dogs in an attempt to supply blood to the myocardium through a skin flap. All except 2 dogs survived the initial operation. A tubed pedicle skin graft was raised from the abdominal and chest walls, based on the region of the 5th and 6th ribs near the apex of the heart. The tube was passed through the pleural space and pericardium, the distal end opened out and sutured to the ventricles, about one-third of the area of such ventricle being covered. The average size of the flaps was 16 cm. long and 9 cm. wide at the base. That a good vascular anastomosis may develop between heart muscle and skin pedicle was demonstrated by the flow of an injected dye and an opaque medium from the descending branch of the left coronary artery into the pedicle. [A radiograph of this is reproduced.] The anastomosis was shown to be sufficient, in one instance, to keep the pedicle alive for a month after the base of the pedicle had been divided at a second operation.

The authors do not know of any previous attempt to supply blood to the myocardium through a skin flap.

Bryan P. Moore

Clinical Evaluation of 1-Hydrazinophthalazine (C-5968) in Hypertension With Special Reference to Alternating Treatment with Hexamethonium. R. L. JOHNSON, E. D. FREIS, and H. W. SCHNAPER. *Circulation*, **5**, 833–841, June, 1952.

The phthalazine derivative 1-hydrazinophthalazine ("C-5968") depresses blood pressure and, in contrast to other hypotensive agents, causes an increase in renal blood flow. It can be given by mouth. The development of side-effects—headache, palpitations, dizziness, weakness—and tolerance could be obviated to a certain extent by giving the drug at wide intervals and by slow increases in dosage. In contrast to the poor results obtained with C-5968 alone, it became apparent that this drug was more effective than any other in maintaining the hypotensive action of hexamethonium when given midway between two parenteral doses of the latter; moreover, it appeared to potentiate the action of hexamethonium, as well as that of veratrum viride. *A. Paton*

Angina Pectoris as a Symptom of Spontaneous Hypoglycaemia. [In English]. P. I. HALONEN and E. TAIPALE. *Cardiologia*, **20**, 243–249, 1952.

At the Wihuri Hospital, Helsinki, 5 patients with angina pectoris stated that their symptoms appeared only several hours after a meal and that food relieved the pain. In all cases a glucose tolerance test showed that marked reactive hypoglycæmia followed about 2 hours after the ingestion of glucose. Anginal pains occurred during this period of hypoglycæmia and one patient showed electrocardiographic changes. The symptoms and signs were immediately relieved by taking sugar. These patients

were seen during the course of one year; 18 months to 2 years later it was found that the advice to take more frequent meals had caused relief of symptoms in all.

H. E. Holling

The Pathogenesis of Spontaneous Cardiac Rupture. S. WESSLER, P. M. ZOLL, and M. J. SCHLESINGER. *Circulation*, **6**, 334–351, Sept., 1952.

An analysis of published figures showed that among 2609 patients dying in 29 general hospitals from acute myocardial infarction the incidence of cardiac rupture was about 9%, and was somewhat greater in women than in men. Similar conclusions were drawn by the authors from an unselected series of 1641 necropsies, in which the myocardium and coronary arteries were studied by injection and dissection, the incidence of rupture being 1·2% in the whole series, and 7% in the group with acute myocardial infarction. This survey showed that rupture usually develops within 2 weeks of acute infarction and is favoured by persisting arterial hypertension or episodes of unusual effort; there is, as a rule, no previous history of infarction or congestive heart failure. From the pathological examination it was concluded that rupture supervenes where the zone of infarction is transmural and of recent origin, with a poor collateral blood supply and absence of fibrosis in at least part of the infarcted area. Most of the drugs commonly used in the treatment of patients with acute infarction are unlikely to cause rupture, but vasopressin, which is occasionally given in order to combat severe hypotension, should not be used, for it is not only a powerful pressor agent but also a potent constrictor of the coronary arteries.

An extensive bibliography is appended.

Adrian V. Adams

Cholesterol Tolerance in Coronary Thrombosis. I. WANG. *Brit. med. J.*, **1**, 1278–1281, June 14, 1952.

In this work from the Victoria Infirmary, Glasgow, the author describes an investigation in which 50 patients, who had fasted overnight, were given 5·0 g. of cholesterol in 25 g. of margarine. The blood cholesterol content was estimated, fasting, and at 2, 4, 6, and 8 hours after the test doses. The patients were divided into 3 groups: Group 1 consisted of 20 normal controls; Group 2 of 12 patients who were suffering from Type 2 nephritis, diabetes mellitus, or myxœdema. Group 3 consisted of 18 patients with atherosclerosis, 15 also had coronary thrombosis.

The cases in Group 2 showed significant increases in the serum cholesterol level, apart from those with myxœdema on adequate thyroid therapy. The results in Groups 1 and 3 did not show any significant difference. The author submits that these results support the belief that the restriction of cholesterol in the diet of patients with coronary thrombosis serves no useful purpose. He also point out that despite the low-cholesterol diet which rationing has imposed in Great Britain for over 10 years, the incidence of coronary thrombosis continues to increase.

Peter Harvey

Cor Pulmonale Resulting from Deformities of the Chest. [In English]. S. SAMUELSSON. *Acta med. scand.*, **142**, 399–408, April 30, 1952.

At the University Hospital, Copenhagen, 41 patients with kyphoscoliosis were examined and the records of 62 dead patients who were known to have suffered from kyphoscoliosis during life were studied in order to determine the incidence of cor pulmonale in such cases. Dyspnœa was an early symptom in 85%, and the pulmonary second sound was accentuated in one-third. Electrocardiograms were taken in 70 cases and in 27 there were signs (chiefly those of right axis deviation) that were considered to signify right heart "strain"; left axis deviation was shown in 16. Of the 62 deaths the cause of death was cardiac failure in 60%, the average age at death being 46 years. Necropsy had been performed in 10 cases, in all of which the right ventricle was hypertrophied.

C. W. C. Bain

Mechanism of Syncope and Action of Drugs in Complete Heart Block. M. H. NATHANSON and H. MILLER. *Calif. Med.*, **76**, 370–375, June, 1952.

Rational treatment of Adams-Stokes seizures depends on the underlying cardiac mechanism, that is, on whether the attacks are due to ventricular asystole on the one hand, or to ventricular tachycardia or fibrillation on the other. An abrupt onset without any premonitory disturbances of rhythm and the absence of any periods of ventricular arrhythmia in an electrocardiogram taken between attacks suggest that ventricular asystole is the causal factor. Conversely, ventricular arrhythmia as a causal factor is suggested by periods of arrhythmia preceding the attack, and a routine electrocardiogram, especially if long strips are taken, may show periods of ventricular extrasystole.

In the treatment of Adams–Stokes seizures due to ventricular systole isoprenaline is recommended, the route of administration depending on the patient's condition. Usually a subcutaneous injection of 0·14 to 0·2 mg. is given, but in the presence of actual syncope 0·02 mg. is given by intracardiac injection, and if syncope is impending 0·02 mg. is given intravenously. In the treatment or prevention of attacks associated with ventricular arrhythmia neither quinidine nor procaine amide is recommended, because these drugs tend to increase ventricular irritability and thereby convert a ventricular tachycardia into a fibrillation, or they exacerbate the latter. Isoprenaline is preferred in these cases also, because it does not exert any unfavourable effect upon ventricular fibrillation; it should certainly be used in those cases in which the causative factor of the seizure cannot be determined.

William A. R. Thomson

Surgical Closure of an Aortic Septal Defect. R. E. GROSS. *Circulation*, **5**, 858–863, June, 1952.

The author describes a case in which an aortic septal defect was treated surgically with success. He discusses the similarity between this condition and patent ductus

arteriosus, and emphasizes the difficulty of preoperative differential diagnosis. In patients suffering from an aortic septal defect the thrill is palable in the pulmonary artery at a much lower level than it is in cases of patent ductus arteriosus and is not obliterated by pressure on the area of the ligamentum arteriosus. In the case described closure was achieved by ligation of the communication with tape. The author states that access through a left interior thoracotomy proved difficult.

J. R. Belcher

An Evaluation of Intracardiac Angiocardiography. G. C. SUTTON, G. WENDEL, H. G. WEDELL, and D. C. SUTTON. *Amer. J. Roentgenol.*, **67**, 596–601, April, 1952.

The authors have compared two methods of angiocardiography: (1) by intracardiac catheterization; and (2) by the more usual technique of injection through a vein. The intracardiac technique was employed on 36 patients, all over 16 years of age, and the venous injection technique on 47.

The advantages of the direct procedure include high concentration of the opaque medium at the site of the investigation, and a clear field unobstructed by shadows of the medium in the right antrium and large veins. The dye can, if desired, be injected directly into the pulmonary artery. Accurate timing of the radiographs can be more easily achieved, and good films can be obtained with a relatively simple low-powered apparatus, the cassettes being hand-operated. The disadvantages are the slightly longer time required for carrying out the catheterization, the greater risk of reaction due to concentration of an irritant medium, and the risk of infection resulting from a slightly more elaborate surgical procedure. Transient arrhythmia was noticed in about one-third of the patients, and there was one death. *A. M. Rackow*

Congenital Pulmonic Stenosis with Open Foramen Ovale in Infancy—Report of Five Proved Cases. R. P. JOHNSON and E. E. JOHNSON. *Amer. Heart J.*, **44**, 344–359, Sept., 1952.

The clinical and pathological features of congenital pulmonic stenosis with an open foramen ovale are described. The stenosis is usually valvular, and of severe degree. This results in considerable right ventricular hypertrophy, with systolic pressures which may exceed the systemic systolic pressure. As right atrial pressure increases, a right-to-left shunt develops; hence cyanosis may not be apparent until some months or even years after birth. Examination reveals signs of pulmonary stenosis with central cyanosis. Radiographs show poststenotic dilatation of the pulmonary artery and oligæmic lung fields. The electrocardiogram is strongly right-sided.

Five illustrative cases are described, all of which were fatal. In 2 cases death followed a respiratory infection and in the remainder it was heralded by paroxysmal dyspnœa. The serious prognostic significance of the latter is stressed, and the authors regard it as constituting an urgent indication for valvotomy. *D. Weitzman*

Treatment of Peripheral Arterial Obliterative Diseases and Their Complications by Arterial Infusions of Histamine. I. MUFSON. *Amer. J. Med.*, **12**, 680–687, June, 1952.

The author discusses the treatment of occlusive vascular disease involving the lower extremities with histamine administered by slow drip into the femoral artery; 2·75 mg. of histamine phosphate was dissolved in 500 ml. of normal saline and infused at the rate of 2 to 5 drops per heart beat. The immediate effects were an erythema from toes to groin, an increase in skin temperature, and filling of superficial veins. Not infrequently the infusion was followed by pain which necessitated termination of the procedure unless a regional nerve block was employed. The injections were given weekly or bi-weekly, the total number varying from 4 to 10.

Three groups of patients were studied. Group 1 consisted of 107 subjects with absent popliteal pulses; Group 2, 10 subjects with no palpable femoral pulses; and Group 3, 16 patients with severe infected ischæmic lesions. The results were judged by improvement in walking distance and by decrease in nocturnal pain. In Group 1 the improvement was very good in 53%, good in 36%, and absent in 11%. In Group 2 the improvement in walking was good in 7 patients and absent in 3. In Group 3 severe infection was significantly improved when antibiotics were added to the infusion solution, and resting pain was abolished in all but one of the 16 patients.

The authors consider that intra-arterial histamine is a more effective vasodilator than either tolazoline given by the same route, or sympathectomy, although the effect of the latter is more lasting. *J. F. Goodwin*

Spatial Vectorcardiography. ARTHUR GRISHMAN and LEONARD SCHERLIS. W. B. Saunders Co., Philadelphia, 1952.

In this monograph the opening chapters describe the theoretical problems of vectorcardiography and the principles are clearly presented and discussed. Relatively little space is devoted to techniques and apparatus, so that the many difficulties of the method are not stressed.

The normal spatial vectorcardiogram is described and well illustrated, and the following sections deal with the common pathological variations. It is perhaps unfortunate that the rare case is often used to illustrate a common condition; this is particularly apparent in the chapter on right ventricular hypertrophy. All chapters are profusely illustrated and the vectorcardiograms are accompanied in most cases by the appropriate electrocardiograms. The standard of reproduction does not always do justice to the high quality of the text; QRS loops are clear in most illustrations but the P and T waves are rarely so.

An overall review of the subject is attempted with success. The authors emphasize the value of an understanding of the concepts of spatial vectorcardiography in the study of routine electrocardiography, and the interrelation of the two forms of recording the electrical activity of the heart is stressed throughout.

Wallace Brigden